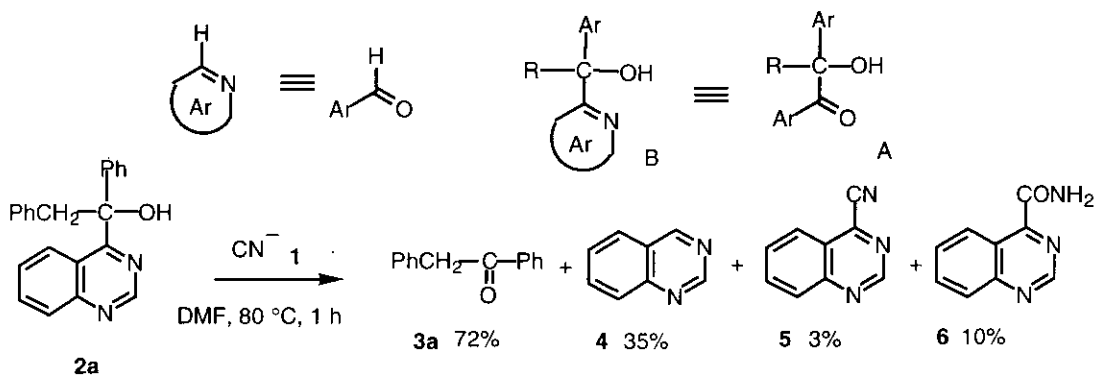
CARBON-CARBON BOND CLEAVAGE OF α-HYDROXYBENZYL-HETEROARENES TO KETONES AND HETEROARENES BY CATALYTIC ACTION OF CYANIDE ION BASED ON RETRO-BENZOIN CONDENSATION

Akira Miyashita,* Yumiko Suzuki, Yuki Takemura, Ken-ichi Iwamoto, and Takeo Higashino

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

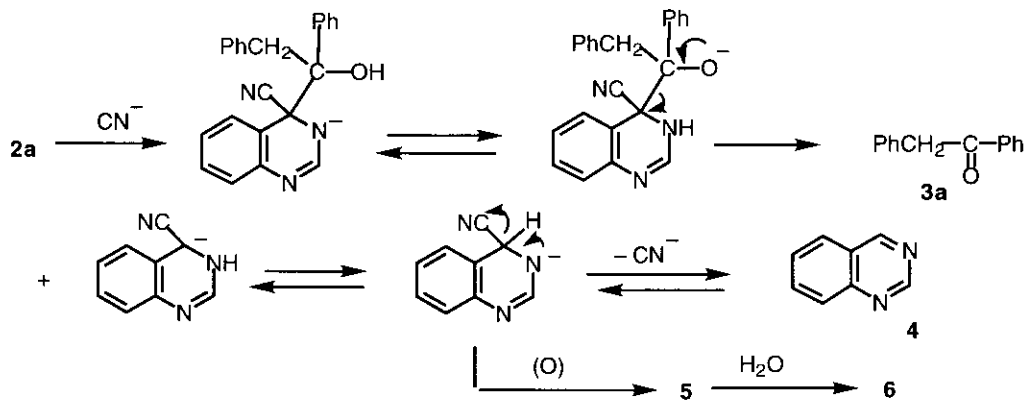
Abstract —— Treatment of 4-(α-benzyl-α-hydroxybenzyl)quinazoline (**2a**) with potassium cyanide in DMF resulted in carbon-carbon bond cleavage to give benzyl phenyl ketone (**3a**) and quinazoline (**4**). Similar results were obtained with other 4-(α-hydroxybenzyl)quinazolines (**2b-f** and **7a**). This reaction proceeds through retro-benzoin condensation. This condensation also proceeded in pyrazolopyrimidine (**9a**) triazolopyrimidine (**10a**), quinoxaline (**11a**), and benzimidazole (**12a**), and the imidazolium salt (**16**) was an effective catalyst.

We have reported that substituted benzoins (A) catalytically decompose to ketones and aldehydes in the presence of cyanide ion.[1] This carbon-carbon bond cleavage proceeds through retro-benzoin condensation. In previous papers, we have shown that the chemical behavior of heteroarenes, in particular quinazolines and pyrazolopyrimidines, is similar to that of aromatic aldehydes.[2] Namely, the carbon-nitrogen double bond (C=N) of heteroarenes behaves like a carbonyl group (C=O). From this viewpoint, the structures of heteroarenes having an α-hydroxybenzyl group at the α-position of the nitrogen are similar to those of benzoins. It was thus expected that carbon-carbon bond cleavage might be catalyzed by cyanide ion. To examine the similarity between benzoins (A) and the α-hydroxybenzylheteroarenes (B), retro-benzoin condensation was investigated.[3]



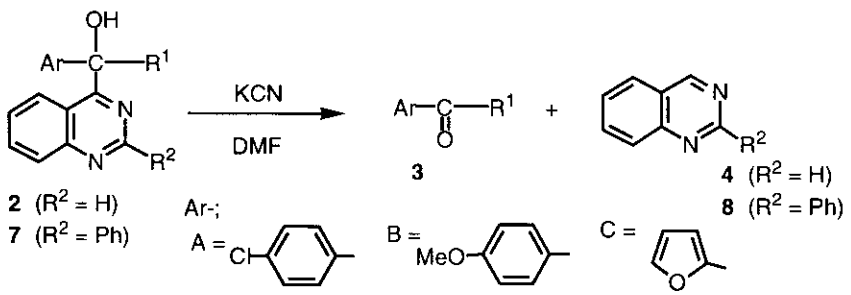
Scheme 1

When 4-(α-benzyl-α-hydroxybenzyl)quinazoline (**2a**) was treated with potassium cyanide in DMF at 80 °C for 1 h, benzyl phenyl ketone (**3a**) and quinazoline (**4**) were the main products, together with 4-quinazolinecarbonitrile (**5**) and 4-quinazolinecarboxamide (**6**). An attempt at carbon-carbon bond cleavage of **2a** in the presence of base alone was unsuccessful. Namely, treatment of **2a** with K_2CO_3 in DMF resulted in recovery of the starting **2** in 96 % yield. This result indicates that the carbon-carbon bond cleavage requires the action of cyanide ion. We considered that the products (**3** and **4**) were formed through retro-benzoin condensation, as expected. The compound (**5**) was formed through addition of **4** with cyanide ion, followed by oxidation. Hydrolysis of **5** resulted in the formation of **6**. The formation mechanism of **3a** and **4** may be as shown in Scheme 2, based on retro-benzoin condensation.



Scheme 2

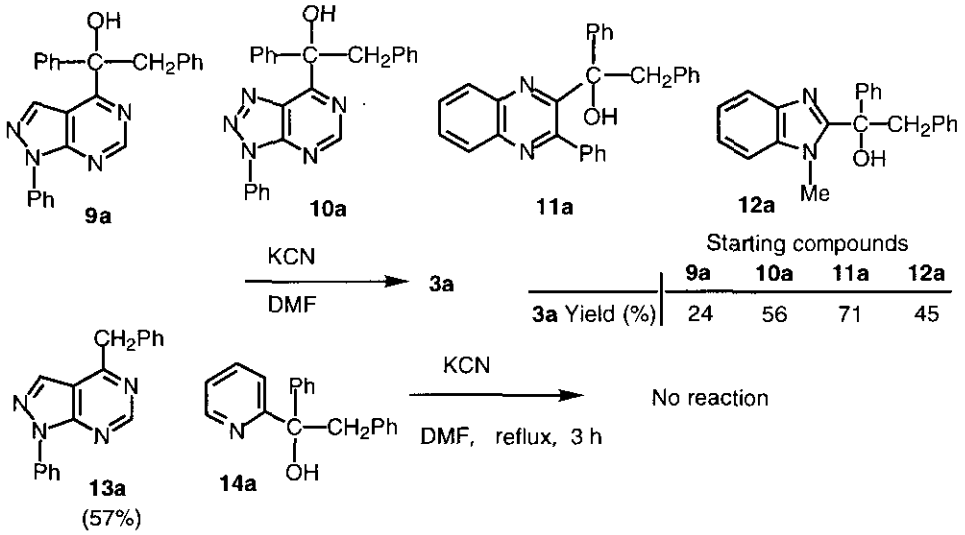
To determine the scope and limitations of this retro-benzoin condensation, the reaction of several heteroarenes was examined. Among quinazolines, compounds (**2**) and (**7**) having an α-hydroxybenzyl moiety at the 4-position underwent carbon-carbon bond cleavage with potassium cyanide to give the corresponding ketones (**3**) and quinazolines (**4** or **8**), as shown in Scheme 3.



				Reaction Conditions		Product; Yield (%)			
	Ar	R^1	R^2	Temp. (°C)	Time (h)	**3**		**4** or **8**	
2b	A	$PhCH_2$	H	80	1	**3b**	68	**4**	—
2c	B	$PhCH_2$	H	80	1.5	**3c**	78	**4**	6
2d	B	Ph	H	reflux	2	**3d**	79	**4**	—
2e	B	Me	H	80	1	**3e**	70	**4**	55
2f	C	$PhCH_2$	H	80	1	**3f**	73	**4**	22
7a	B	$PhCH_2$	Ph	reflux	1	**3c**	77	**8**	68

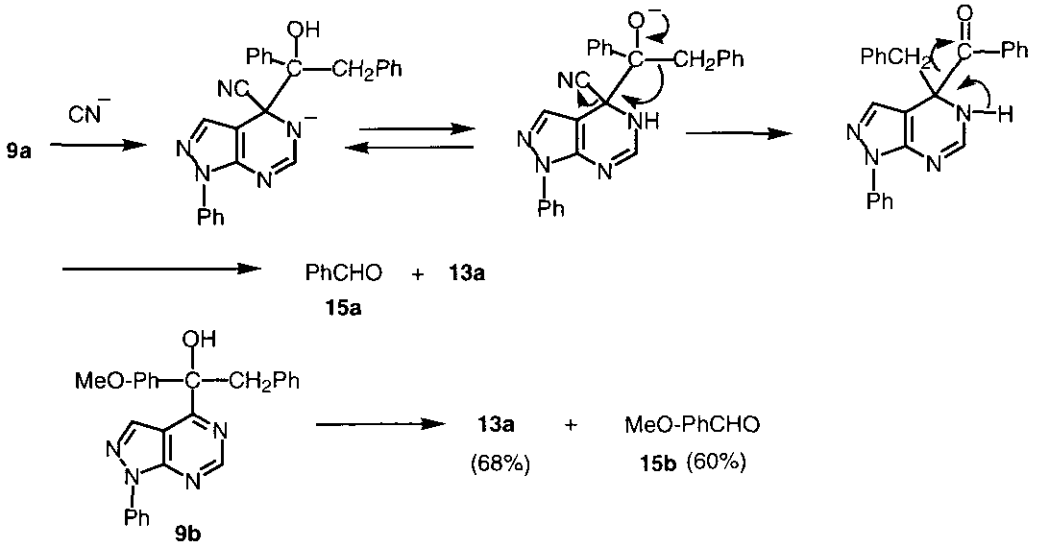
Scheme 3

Such carbon-carbon bond cleavage was also observed to proceed in pyrazolopyrimidine (**9a**), triazolopyrimidine (**10a**), quinoxaline (**11a**), and benzimidazole (**12a**)[4] in the presence of cyanide ion to give benzyl phenyl ketone (**3a**) in moderate yields. However, similar treatment of the pyridine (**14a**) resulted in recovery of the starting compound (**14a**). The nucleophilic reactivities of pyridines are known to be low compared with those of other heteroarenes having one or two nitrogens in the six-membered ring system.[5]



Scheme 4

In the case of pyrazolopyrimidine (**9a**), the yield of the ketone (**3a**) was low because of the formation of benzylpyrazolopyrimidine (**13a**) in 57% yield.[6] Compound (**13a**) might be obtained through benzyl migration catalyzed by cyanide ion, as shown in Scheme 5, because in the absence of potassium cyanide, the benzyl compound (**13a**) was not obtained. The rearrangement of the benzyl group was also observed in another pyrazolopyrimidine (**9b**) on similar treatment, to give benzylpyrazolopyrimidine (**13a**) in 68% yield.

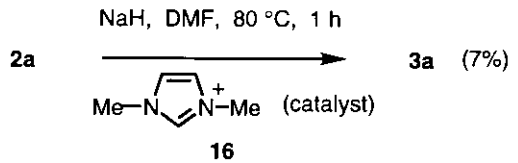


Scheme 5

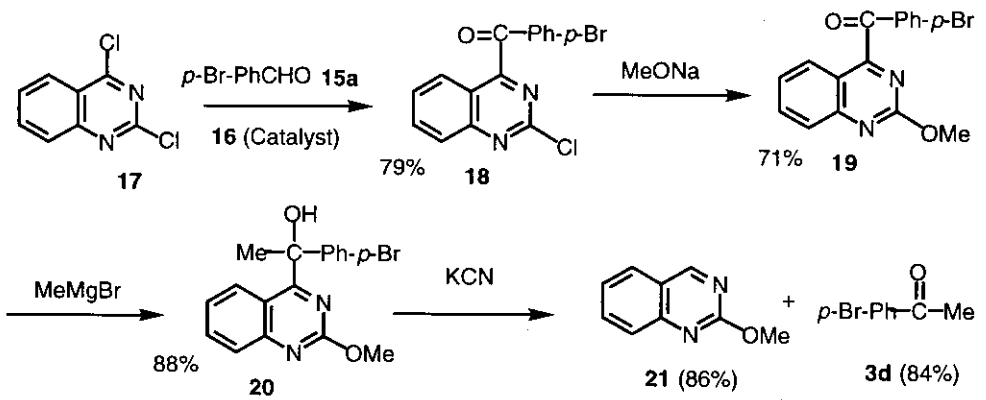
In this reaction, *p*-anisaldehyde (**15b**) was formed in 60% yield.[7] This result is consistent with the formation pathway proposed by us.

We have already reported that imidazolium iodide (**16**) catalyzes benzoin and retro-benzoin condensations, like cyanide ion.[1,8] However, **2a** was decomposed by the catalytic action of **16** to give **3a** in only 7% yield. One of the reasons for the low activity of **16** may be the difficulty of attack at the C-4 position of quinazoline because of the bulkiness of the catalyst.

These results indicate that an α-hydroxybenzyl moiety on heteroarenes can be used as a protecting group, and this group attached at a π-deficient position on heteroarenes can be easily removed by the catalytic action of cyanide ion. This reaction was applied to synthesize 2-substituted quinazolines from 2,4-dichloroquinazoline (**17**), as shown in Scheme 7.[9] Namely, this compound (**17**) reacted with 1.2 molar equivalents of *p*-bromobenzaldehyde (**15a**) in the presence of the imidazolium salt (**16**) to give 2-chloro-4-(*p*-bromobenzoyl)quinazoline (**18**).[10] The quinazoline (**18**) was allowed to react with



Scheme 6



Scheme 7

sodium methoxide to give 2-methoxy-4-(*p*-bromobenzoyl)quinazoline (**19**). Treatment of **19** with methylmagnesium bromide gave the quinazoline (**20**) having an α-hydroxybenzyl moiety at the 4-position. The retro-benzoin condensation of the quinazoline (**20**) furnished 2-methoxyquinazoline (**21**)[11] and the ketone (**3g**). The sequential reaction proceeds owing to the difference of reactivity between the 2- and 4-positions of quinazolines, and this sequence shows that the α-hydroxybenzyl moiety can be used as a protecting group. We have established a method for synthesis of 2-substituted quinazolines from 2,4-dichloroquinazoline (**17**).

On the basis of retro-benzoin condensation and the similar reaction behavior of α-hydroxybenzyl-heteroarenes (B) and benzoins (A), we found two carbon-carbon bond cleavage reactions, *i,e.*, decomposition of an α-hydroxybenzyl moiety on a heteroarene to afford a ketone and heteroarene, and rearrangement of benzyl group with release of arenecarbaldehyde. Both reactions are catalyzed by cyanide ion.

REFERENCES AND NOTES

1. A. Miyashita, Y. Suzuki, Y. Okumura, and T. Higashino, *Chem. Pharm. Bull.*, 1996, **44**, 252.
2. (*a*) T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.*, 1974, **22**, 2493; (*b*) *idem*, *ibid.*, 1976, **24**, 238; (*c*) T. Higashino, Y. Matsushita, M. Takemoto, and E. Hayashi, *ibid.*, 1983, **31**, 3951.
3. Typical procedure: A solution of 4-(α-phenyl-α-hydroxybenzyl)quinazoline (**2a**, 326 mg, 1 mmol) and KCN (72 mg, 1.1 mmol) in 10 ml of DMF 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 dried over Na_2SO_4 and concentrated. The residue was purified on a column of SiO_2 with hexane and $CHCl_3$. The fraction eluted with hexane gave benzyl phenyl ketone (**3a**, 141 mg, 72%). The first fraction eluted with hexane and $CHCl_3$ (2:1) gave 4-quinazolinecarbonitrile (**5**, 4 mg, 3%) and the second fraction gave quinazoline (**4**, 45 mg, 35%). The fraction eluted with $CHCl_3$ gave 4-quinazolinecarboxamide (**6**, 17 mg, 10%).
4. α-Benzyl-α-hydroxybenzylheteroarenes were prepared from the corresponding aroylheteroarenes by treatment with benzylmagnesium chloride. **2a**: Colorless granules (ether-hexane), mp 113-114 °C. *Anal.* Calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28. Found: C, 76.52; H, 5.02; N, 14.26. Ir (KBr) cm^{-1}: 3300-3500 (OH). ^{1}H-Nmr ($CDCl_3$): 3.69 (1H, d, J = 14, CH_2), 4.05 (1H, d, J = 14, CH_2), 4.03 (1H, s, OH), 6.80-7.78 (13H, m, aromatic H), 7.99-8.20 (2H, m, N-Ph-*o*), 8.25 (1H, s, C^3-H), 8.92 (1H, s, C^6-H).
5. The reactivities of pyridines are summarized in the literature; "*Comprehensive Heterocyclic Chemistry*" ed. by A. R. Katritzky and C. W. Rees, Pergamon Press (Oxford), **1984**, Vol. 2, 165.
6. Treatment of 4-(α-phenyl-α-hydroxybenzyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**9a**, 392 mg, 1 mmol) with KCN (72 mg, 1.1 mmol) in DMF (5 ml) at 80 °C for 1 h gave benzyl phenyl ketone (**3a**, 48 mg, 24%) and 4-benzyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**13a**, 162 mg, 57%). **13a**; Colorless needles from hexane, mp 100-101 °C (lit., 100-101 °C). T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, 1979, **94**, 666.
7. Treatment of 4-[α-(*p*-methoxyphenyl)-α-hydroxybenzyl)]-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**9b**, 422 mg, 1 mmol) with KCN (72 mg, 1.1 mmol) in DMF (5 ml) at 80 °C for 1 h gave **13a** (172 mg, 68%) and *p*-anisaldehyde (**15b**, 82 mg, 60%).
8. A. Miyashita, Y. Suzuki, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*, 1994, **42**, 2633.
9. In general, 2-substituted quinazolines are prepared by reaction of 2-chloroquinazoline with nucleophiles. 2-Chloroquinazoline is prepared by chlorination of 2-hydroxyquinazoline.[a] To our knowledge, it is not easy to prepare 2-hydroxyquinazoline by ring closure from *o*-aminobenzaldehyde and urea.[b] In contrast, 2,4-dihydroxyquinazoline and 2,4-dichloroquinazoline (**17**) are easily prepared. (*a*) S. Niementowski, *J. Prakt. Chem.*, [2], 1895, **51**, 564; (*b*) S. Gabriel and T. Posner, *Ber.*, 1895, **28**, 1029
10. (*a*) A. Miyashita, H. Matsuda, C. Iijima, and T. Higashino, *Chem. Pharm. Bull.*, 1990, **38**, 1147; (*b*) *idem*, *ibid.*, 1992, **40**, 43; (*c*) A. Miyashita, H. Matsuda, Y. Suzuki, K. Iwamoto, and T. Higashino, *ibid.*, 1994, **42**, 2017.
11. G. Stefanovic, L. J. Lorenc, and M. L. Mihailovic, *Rec. Trav. Chim.*, 1961, **80**, 149 (*Chem. Abstr.*, 1961, **55**, 24764c).

Received, 15th August, 1996