Reductive Coupling of Benzoyl Cyanide and Carbonyl Compounds by Aqueous Ti(III) Ions. A New Convenient and Selective Access to the Less Stable Mixed Benzoins

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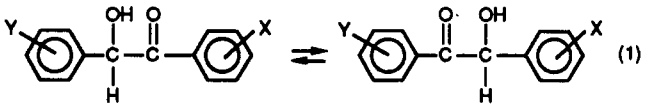
The reactive species formed by the Ti(III) ion reduction of benzoyl cyanide (1) adds to the C-atom of carbonyl compounds **2** under simple experimental conditions. The intermediate 1,2-diols **3** are smoothly converted, without isolation, into the less thermodynamically stable mixed benzoins **4**, which are not accessible by the classical benzoin condensation. The possible mechanisms involved in the reaction are discussed.

Introduction

One of the longest known reactions in organic chemistry is the benzoin condensation.[1,2] The mechanism of this reaction (Scheme I) has been firmly established[3] as that initially proposed by Lapworth in 1903.[4] Cyanide ion serves a catalytic role in the generation of a cyanohydrin carbanion, which is synthetically equivalent to the unavailable benzoyl anion. Since the discovery of the benzoin condensation, both the versatility[5] of the reaction and the yield of symmetrical[2,6] and unsymmetrical[2,7] benzoins have been improved. However, in the condensation of two aldehydes of widely different character, only the more stable form (A, eq 1) of the two isomeric mixed benzoins,



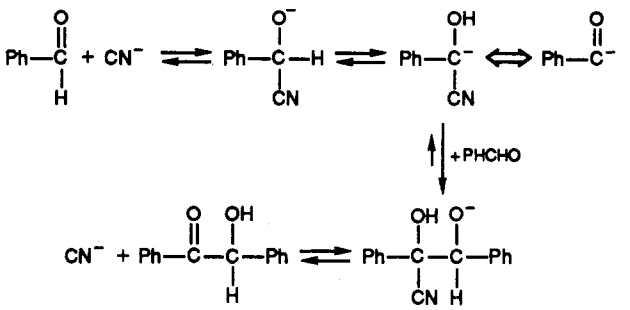
A B (1)

Y = H, Cl, Br; X = CH_3, OCH_3, OH, $(CH_3)_2N$

A and B, is isolable. The production of A, in which the carbonyl group is adjacent to the phenyl ring with the more electron-donating substituent, is consistent with the reversibility of the reaction and the relative stability of the carbonyl groups in the possible products.[8]

One established procedure[1,9] for the synthesis of the less thermodynamically stable mixed benzoin (B) involves the addition of an excess of Grignard reagent to a cyanohydrin or to a protected cyanohydrin of an aromatic aldehyde.[10–12] An improved method for the synthesis of

Scheme I



B involves the generation of a "masked" acyl carbanion, which reacts with aliphatic[13–15] and aromatic[15,16] aldehydes or ketones.[13,15] Reduction[17] of unsymmetrical benzils, contrary to a previous report,[18] is not chemoselective.

Of the many reports of syntheses of benzoin B, only a few are both simple and general. In addition, all of the syntheses involve masking and unmasking steps, which do not give satisfactory results[16] in all cases. We wish to report a new, simple, and versatile procedure for the synthesis of benzoins B (eq 1, Y = H). The reaction can also be extended to the preparation of α-hydroxy ketones.[19]

Results and Discussion

In the course of our studies,[20] we have found that when benzoyl cyanide (1) is allowed to react with an aqueous acidic $TiCl_3$ solution in CH_3COOH, benzil dicyanohydrin is produced by reductive coupling. When the reaction is carried out in the presence of acetone[20] or acetaldehyde,[21] the corresponding 1,2-diols (3) (Scheme II) are produced. The intermediate α-CN-ketyl radical [I], formed by inner-sphere electron-transfer (ET)[22] from Ti(III) to 1, can be regarded as a masked benzoyl radical. In general, benzoyl

(1) Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269.
(2) (a) Barton, D. H. E.; Ollis, W. D. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, 1979, Vol I, p 1142. (b) March, J. *Advanced in Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985; p 859.
(3) Kuebrich, J. P.; Schowen, R. L.; Wang, M. S.; Lupes, M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1214.
(4) (a) Lapworth, A. J. *J. Chem. Soc.* **1903**, *83*, 995. (b) Lapworth, A. J. *Ibid.* **1904**, *85*, 1206.
(5) Stetter, H.; Ramsch, R. Y.; Kuhlmann, H. *Synthesis* 1976, 733.
(6) Solodar, J. *Tetrahedron Lett.* **1971**, *12*, 287.
(7) Hakimelahi, G. H.; Boyce, G. B.; Kasmai, H. S. *Helv. Chim. Acta* **1977**, *60*, 342.
(8) (a) Merz, K. W.; Plauth, D. *Chem. Ber.* **1957**, *90*, 1744. (b) Semerano, G. *Gazz. Chim. Ital.* **1941**, *71*, 447.
(9) Copper, D. J.; Owen, L. N. *J. Chem. Soc. (C)* **1966**, 536.
(10) (a) Elphimoff-Felkin, I. *Bull. Soc. Chim. Fr.* **1955**, 784. (b) Elphimoff-Felkin, I.; Verrier, M. *Ibid.* **1967**, 1047.
(11) Slosser, M.; Brich, Z. *Helv. Chim. Acta* **1978**, *61*, 1903.
(12) Krepski, L. R.; Heilmann, S. M.; Rasmussen, J. K. *Tetrahedron Lett.* **1983**, *24*, 4075.
(13) Hunig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062.
(14) Hamana, M.; Endo, T.; Sacki, S. *Tetrahedron Lett.* **1975**, *16*, 903.
(15) Koeingkramer, R. E.; Zimmer, H. *Tetrahedron Lett.* **1980**, *21*, 1017.
(16) Rozwadowska, M. R. *Tetrahedron* **1985**, *41*, 3135.
(17) Heilmann, S. M.; Rasmussen, J. K.; Smith, H. K., II, *J. Org. Chem.* **1983**, *48*, 987.
(18) van Es, T.; Backeberg, O. G. *J. Chem. Soc.* **1963**, 1371.
(19) Aromatic α-hydroxy ketones are called benzoins. Similar compounds containing aromatic heterocyclic nuclei are also classed as benzoins. If one nucleus is aliphatic and the other is aromatic, the products are called α-hydroxy ketones (See refs 1 and 2).
(20) Clerici, A.; Porta, O.; Riva, M. *Tetrahedron Lett.* **1981**, *22*, 1043.
(21) Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852.
(22) Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5089.

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Scheme II

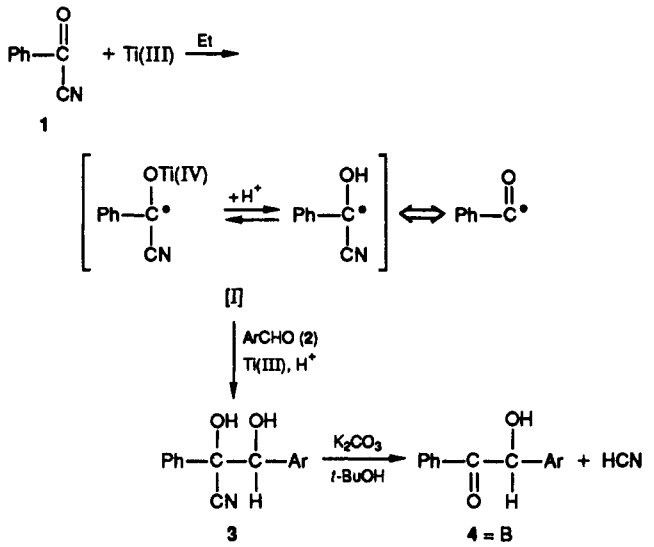


Table I. Yields[a] of Benzoins Isolated from the Ti(III)-Mediated Reaction

PhC(O)CN + ArC(H)O $\xrightarrow{Ti(III),\ H^+\ K_2CO_3}$ PhC(O)C(H)(OH)Ar
1 2a–q 4a–q

entry	Ar	4 (yield %)	mp (°C)	mp Lit. (°C)
a	C_6H_5	45 (28)[b]	134	134[1]
b	4-CH_3-C_6H_4	38	118	117[12]
c	2-CH_3-C_6H_4	36	64	64–5[1]
d	4-OCH_3-C_6H_4	49	89–90	88–9[17]
e	3-OCH_3-C_6H_4	44	80–1	–
f	2-OCH_3-C_6H_4	42	58–9	57–58.5[15]
g	3,4-$(OCH_3)_2$-C_6H_3	40	(oil)	–
h	3,4-(O_2CH_2)-C_6H_3	42	112	–
i	4-OH-C_6H_4	50	186–7	187–9[9]; 173–4[17]
j	2-OH-C_6H_4	40	159–61	148[1]; 160–1[28]
k	4-$(CH_3)_2N$-C_6H_4	36	159–60	159–60[1]
l	4-Br-C_6H_4	37	128–30	126–8[16]
m	4-Cl-C_6H_4	42	111–13	110–3[17]
n	4-CN-C_6H_4	43 (22)[b]	110–1	112–3[15]
o	2-furan	32	119	119[1]
p	3-Py	53	97–9	–
q	2-Py	42[c]	70–1	72–72.5[42]

[a] Yields are based on the amount of starting material 1; the molar ratio PhC(O)CN/ArC(O)H was 1:2. [b] Molar ratio PhC(O)CN/ArC(O)H, 1:1. [c] Isolated as α-diketone.

radicals, σ-type radicals, add to the carbonyl O-atom,[23,24] but the "masked" benzoyl radical, a π-type radical, adds to the carbonyl C-atom. Thus, the reactivity of the masked functionality is inverted compared to that of the unmasked.

For this reason, we centered our interest on the use of intermediate [I] as an acylating agent for the synthesis of those benzoins B (4, Scheme II) that cannot be obtained under "benzoin condensation" conditions because of the reversibility of the reaction. The feasibility of our methodology was greatly enhanced by the facile and mild unmasking procedure (3 → 4), which was accomplished without prior isolation of intermediate diols 3 and, above all, occurred without isomerization to the more stable benzoin A (eq 1). Electrophile 2 can be not only an

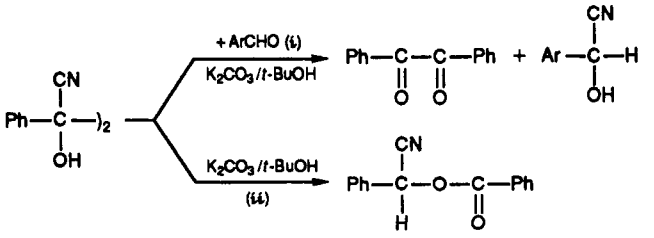
Table II. Yields[a] of α-Hydroxy Ketones Isolated from the Ti(III)-Mediated Reaction

PhC(O)CN + R_1R_2CO $\xrightarrow{Ti(III),\ H^+\ K_2CO_3}$ PhC(O)C(OH)R_1R_2
1 2r–z 4r–z

				yields (%)	
entry	R_1	R_2	molar ratio 1/2	4	5
r	H	CH_3	1:5	28	22
	H	H	1:2	30	7
s	H	C_2H_5	1:5	28	20
	H	C_2H_5	1:2	29	5
t	H	$PhCH_2$	1:2	26	trace
u	CH_3	CH_3	solvent[b]	53	–
v	$-(CH_2)_4-$		cosolvent	34	–
w	$-(CH_2)_5-$		cosolvent	37	–
y	CH_3	2-Py	1:1	44[c]	–
z	CH_3	4-Py	1:1	44[c]	

[a] Yields are based on the amount of starting material 1. [b] Aliphatic ketones were used as solvent (30 mL) or cosolvent (20 mL). [c] See ref 21.

Scheme III



aromatic or a heteroaromatic aldehyde (ArCHO, Table I) but also an aliphatic aldehyde or ketone (R_1R_2CO, Table II).

Allowing a mixture of 1 (10 mmol) and 2 (20 mmol) in glacial CH_3COOH to react with a 15% aqueous acidic $TiCl_3$ solution (22 mmol) at rt for 2 h led to the formation of 3 (threo/erythro, ca. 1:1) and benzil dicyanohydrin (meso, *dl*). Usually, 4 was produced from 3 by vigorous stirring of the crude reaction mixture with solid K_2CO_3 in t-BuOH, at 30 °C for 3–4 h. After workup, flash chromatography of the organic residue afforded 4 in the yields shown in Tables I and II.

The demasking procedure occurred in good yields (>90%) in most of the cases examined; the only exceptions were the reactions of 1 with salicylaldehyde and 2-pyridinecarboxaldehyde. In the former case, a mixture of undesired and unidentified products was formed together with **4j** (see Experimental Section) and, in the latter, **3q** was smoothly converted into 2-pyridin-2-yl-1-phenylethanedione (the great air sensitivity of **4g** has already been reported).[25]

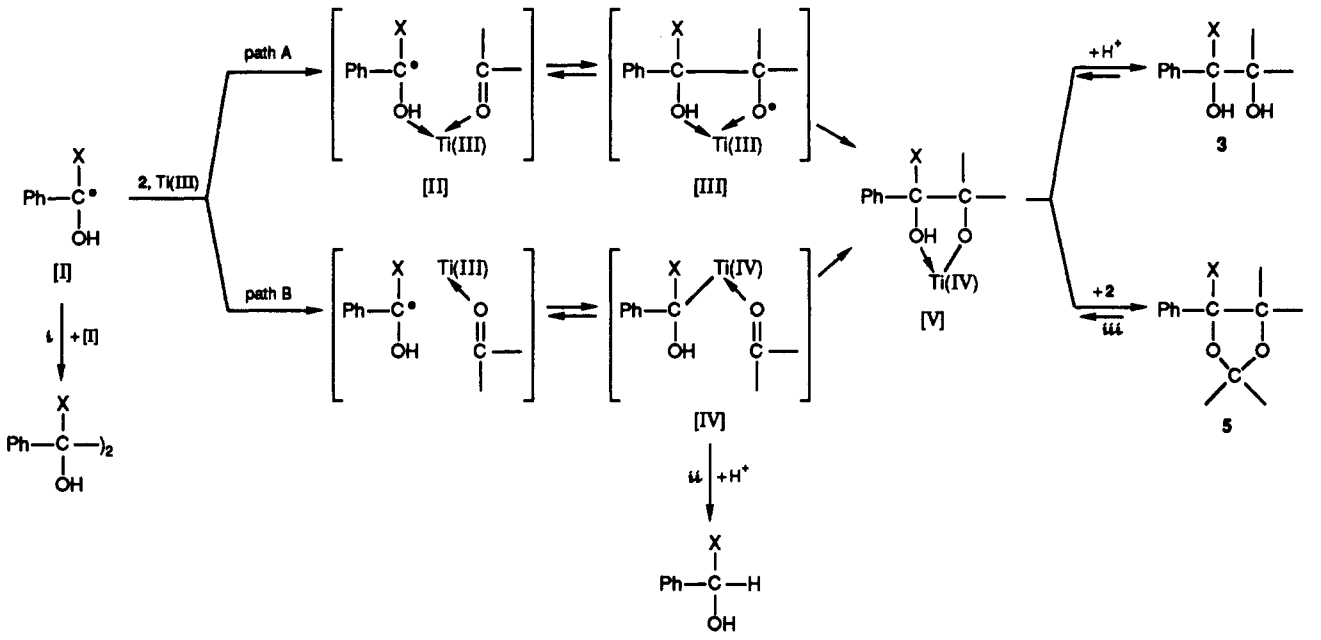
Byproducts of the demasking step were benzil (30–40%), formed by decyanation of benzil dicyanohydrin and, the cyanohydrin of 2 (25–35%), produced by cyanide addition to unreacted 2 (Scheme III, path i). The R_f values of these byproducts permitted an easy purification of 4 by flash chromatography. Low-boiling aldehydes (**2r** and **2s**) were no longer present in the crude reaction mixture at the time of the unmasking procedure and, thus, benzoyl-

(23) (a) Rust, F. F.; Seubold, F. H.; Vaughan, W. E. *J. Am. Chem. Soc.* **1948**, *70*, 3258. (b) Urry, W. H.; Mishihara, A.; Niu, J. H. Y. *J. Org. Chem.* **1967**, *32*, 347. (c) Kuivila, H. G.; Walsh, J. *J. Am. Chem. Soc.* **1966**, *88*, 571. (d) Kuivila, H. G.; Walsh, J. *Ibid.* **1967**, *88*, 576.

(24) Contribution of polar forms [Ph–$\dot{C}$O + R–C(H)O ↔ Ph –$\dot{C}$O + R–$\dot{C}$(H)O$^-$] to the transition state explains the reactivity of acyl radicals with carbonyl compounds.

(25) (a) Ohno, A.; Yasni, S.; Oka, S. *Bull. Soc. Chim. Jpn.* **1980**, *53*, 3244. (b) Buckler, C. A.; Addleburg, J. W.; Glenn, D. M. *J. Org. Chem.* **1955**, *20*, 1350.

Scheme IV[a]



[a] In the present work, X = CN.

mandelonitrile,[26] instead of benzil, was formed from benzil dicyanohydrin as the sole byproduct (Scheme III, path ii). As evidenced in Table I (entries a and n), the yields of **4** increase when the molar ratio of **2**/benzoyl cyanide was increased from 1:1 to 2:1. A ratio higher than 2:1 (Table II, entries r and s) caused the formation of acetals **5** (Scheme IV), which cannot be hydrolyzed under the demasking basic conditions used. Aliphatic ketones (Table II, entries u, v) were poor substrates, and reasonable yields of **4** were obtained only when they were used as solvents or cosolvents. In contrast to the aldehydes, the ketones did not afford ketals, even when they were used in large excess. Although the yields of benzoins (Table I) and α-hydroxy ketones (Table II) do not exceed 53%, there are a number of features that make this new methodology advantageous over the methods in the literature: (a) inexpensive and commercially available starting materials (**1**, **2**, and aqueous acidic $TiCl_3$) are used; (b) the reaction times are short, and the experimental conditions (rt, aqueous solution) are simple; (c) all 17 aromatic aldehydes examined give the corresponding product **4** because all the substituents in the phenyl ring are compatible with the extremely mild conditions used; (d) the benzoins **4e**, **4g,h**, and **4p** were previously unknown. The present method is the procedure of choice for the preparation of **4c**, **4i**, **4k**, and **4o**; the only previous syntheses reported involved the reactions of a Grignard reagent with mandelonitriles and proceeded in yields not better than 47%.[1,9] The other benzoins and α-hydroxy ketones that we prepared by our method have been synthesized in higher yields but under more laborious conditions.[13,15-17,28]

The mechanism postulated in earlier papers[20,21,29] for the Ti(III)-mediated addition of α-X-substituted benzoyl compounds (PhC(O)X, were X = COPh, $COCH_3$, COH, $COOCH_3$, CN) to carbonyls **2** is outlined in Scheme IV (path A). Thermodynamic stabilization of "captodative" radical [I] encourages dimerization[30] (path i). However, the competitive reversible addition of [I] to **2** may be feasible if all the steps of the reaction proceed in close proximity to the metal ion. An "assisted five-membered" transition state [II] increases the reactivity and favors both the "quasiintramolecular" addition and the further reduction of the alkoxy radical [III], which is then rapidly removed from the equilibrium before it can fragment.[31] Both the oxophilicity and Lewis acidity of titanium ion are well evidenced by the easy acetalization of [V] (path iii),[29a,32] which occurs whenever the molar ratio of **2**/benzoyl cyanide is higher than 2.[33,34]

In an alternate reaction mechanism (Scheme IV, path B), [I] is in equilibrium with the organotitanium intermediate [IV], in which the Ti(III) ion acts as a radical-type metal toward [I] and as a complexing agent toward **2**. Only a strictly organized "assisted four-membered" transition state, such as [IV], can explain the favored C–C bond formation over the metal–carbon bond protolysis (path ii). In fact, in aqueous acidic solution (pH $\leq$ 1), metal–carbon bonded species are known to quickly decompose,[35] via reaction with hydrogen ion but, in our case,

(26) The anion of benzoylmandelonitrile has been repeatedly invoked as an intermediate[27] in the reaction of aromatic α-diketones with cyanide ion, but the intermediate, per se, has never been isolated in alcoholic solvents. A more detailed study of the equilibra involved in the formation of benzoylmandelontrile in t-BuOH will be published in due time.

(27) Reference 2a, p 1201.

(28) Koenigkramer, R. E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994.

(29) (a) Clerici, A.; Porta, O. *J. Org. Chem.* **1989**, *54*, 3872. (b) Clerici, A.; Porta, O.; Zago, P. *Tetrahedron* **1985**, *42*, 561.

(30) Viehe, H. G.; Mereny, R.; Stella, L.; Janousek, Z. *Angew Chem.* **1979**, *91*, 982.

(31) (a) Walling, C. *Pure Appl. Chem.* **1967**, *15*, 69. (b) Huyser, E. S. *Free Radical Chain Reactions*; Wiley Interscience: New York, 1970; p 229. (c) Kochi, J. K. *Free Radicals*; Wiley Interscience: New York, 1973; Vol II, p 683.

(32) (a) Clerici, A.; Porta, O. *Synth. Commun.* **1988**, 2281. (b) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1992**, *48*, 3867.

(33) It is well documented that acetalization is a reversible process that can be shifted to the side of acetal only by removal of the water formed. Flowers, H. M. *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; London, 1971; p 1029.

(34) The molar ratio R–C(H)O/Ph–C(X)O at which **5** is formed depends on the X-substituent and, above all, on the steric and electronic nature of the aldehyde. With ketones, the formation of **5** has never been observed because of the greater steric hindrance about the reaction center. See refs 29 and 32.

(35) Gold, V.; Pemberton, S. M.; Wood, D. L. *J. Chem. Soc. Perkin Trans. II* **1981**, 1230.

this phenomenon has been observed only to a very small extent.[36] The assumption that coordination of the titanium ion and the aldehyde gives rise to intermediate [IV] is partially supported by our recent work,[37] in which we found that the reducing properties of the metal ion are increased by the presence of acetaldehyde.[38]

Although more detailed studies are needed to better elucidate the reactive intermediates, at present, the practical result is the eventual formation of **3**. Adducts **3** (X = CN) have a peculiar synthetic interest since, after a gentle unmasking procedure, they afford less thermodynamically stable mixed benzoins **4**. In this context, the present reaction may well be considered complementary to the classical benzoin condensation.

Experimental Section

General Methods (see ref 37). General Procedure for Benzoins and α-Hydroxy Ketones Formation (entries a–q and r–w). To a well-stirred solution of aldehyde **2** (20 mmol) and benzoyl cyanide (10 mmol) in CH_3COOH (30 mL) at rt was added, in one portion, 15% aqueous $TiCl_3$ (22 mmol) while N_2 was bubbled through the solution. When ketones were used, they served as solvent or cosolvent. After 2 h, the reaction mixture was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to afford a crude residue containing unreacted **2**, the dimer of benzoyl cyanide, and diols **3** as a mixture of diastereoisomers. Intermediates **3** were not isolated, since partial dehydrocyanation to **4** occurred during their purification on a silica gel column. The procedure of choice for dehydrocyanation, with the exception of **3j**, was as follows: the crude residue, dissolved in t-BuOH (20–40 mL), was stirred with K_2CO_3 (1.4 g, 0.10 mmol) at 35 °C for 4 h. EtOAc (100 mL) was then added to the reaction mixture, and the insoluble K_2CO_3 was filtered off. The filtrate was washed with H_2O, dried, and concentrated in vacuo, and the residue was purified by flash-column chromatography on silica gel with hexane/Et_2O/$CHCl_3$ (from 6:2:2 to 4:3:3). As a rule, benzil, unreacted **2**, benzoins **4**, and the cyanohydrin of **2** were eluted in that order. Benzil, which is formed by dehydrocyanation of benzil dicyanohydrin, was obtained in 30–40% yields, based on starting material **1**; the cyanohydrin of **2** was recovered in 15–30% yield. With low-boiling aliphatic aldehydes (entries r and s) and ketones (entries u–w), benzoylmandelonitrile, instead of benzil, was isolated during the dehydrocyanation of the crude reaction mixture. The elution order from flash-column chromatography was as follows: acetals **5** (entries r,s), benzoylmandelonitrile, and α-hydroxy ketones **4**. The spectroscopic data of unknown benzoins **4**, and of those benzoins for which only elemental analysis and melting point are available in the literature, are reported.

2-Hydroxy-2-(2-methylphenyl)-1-phenylethanone (4c): IR (melt) ν_{max} 3440, 1685, 1250 cm^{-1}; MS *m/z* 226 ($M^{+\cdot}$, 2), 121 (76), 119 (100), 105 (40), 91 (50), 77 (44), 65 (14), 51 (16); ^1H NMR ($CDCl_3$) δ 2.54 (3 H, CH_3, s), 4.4 (1 H, OH, d, *J* = 5.5 Hz, D_2O exchangeable), 6.5 (1 H, CH, d, *J* = 5.5 Hz, s after D_2O exchange), 7.02 (1 H, Ar H, m), 7.1 (1 H, Ar H, m), 7.2 (2 H, Ar H, m), 7.36 (2 H, Ph H, m), 7.5 (1 H, Ph H, m), 7.82 (2 H, Ph H, m).

2-Hydroxy-2-(3-methoxyphenyl)-1-phenylethanone (4e): white crystals, mp 80–1 °C (hexane/EtOAc, 1:1); IR ν_{max} 3400, 1675, 1260 cm^{-1}; MS, *m/z* 242 ($M^{+\cdot}$, 10), 137 (M − PhCO, 60), 136 (40), 135 (100), 109 (137 − CO, m* = 86.7, 35), 107 (135-CO, m* = 84.8, 45), 105 (55), 79 (20), 77 (60), 51 (5); ^1H NMR ($CDCl_3$) δ 3.73 (3 H, OCH_3, s), 4.62 (1 H, OH, d, *J* = 6 Hz, D_2O exchangeable), 5.9 (1 H, CH, d, *J* = 6 Hz, s after D_2O exchange), 6.79 (1 H, Ar H, m), 6.85 (1 H, Ar H, m), 6.92 (1 H, Ar H, m), 7.2 (1 H, Ar H, m), 7.38 (2 H, Ph H, m), 7.5 (1 H, Ph H, m), 7.92 (2 H, Ph H, m). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.20; H, 5.70.

2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-phenylethanone (4g): thick oil; IR (film) ν_{max} 3450, 1680, 1260, 1140, 1030 cm^{-1}; MS, *m/z* 272 ($M^{+\cdot}$, 1.5), 167 (28), 166 (85), 165 (100), 151 (15), 139 (7), 137 (9), 122 (16), 105 (23), 95 (30), 79 (20), 77 (44), 51 (27); ^1H NMR ($CDCl_3$) δ 3.84 (6 H, 2 OCH_3, s), 4.52 (1 H, OH, d, *J* = 5 Hz, D_2O exchangeable), 5.91 (1 H, CH, d, *J* = 5 Hz, s after D_2O exchange), 6.78 (1 H, Ar H, d, *J* = 2 Hz), 6.80 (1 H, Ar H, d, *J* = 9 Hz), 6.91 (1 H, Ar H, dd, *J* = 2, 9 Hz), 7.4 (2 H, Ph H, m), 7.52 (1 H, Ph H, m), 7.92 (2 H, Ph H, m). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.50; H, 5.82.

2-Hydroxy-2-[3,4-(methylendioxy)phenyl]-1-phenylethanone (4h): white crystals, mp 112 °C (EtO_2); IR (KBr) ν_{max} 3440, 1680, 1250 cm^{-1}; MS, *m/z* 256 ($M^{+\cdot}$, 2), 151 (30), 150 (28), 149 (100), 121 (15), 105 (10), 93 (15), 77 (19), 65 (19); ^1H NMR ($CDCl_3$) δ 4.55 (1 H, OH, d, *J* = 6 Hz, D_2O exchangeable), 5.84 (1 H, CH, d, *J* = 6 Hz, s after D_2O exchange), 5.86 and 5.88 (2 H, CH_2, AB system, J_{AB} = 1.5 Hz); 6.73 (1 H, Ar H, d, *J* = 8 Hz), 6.74 (1 H, Ar H, d, *J* = 2 Hz), 6.84 (1 H, Ar H, dd, *J* = 2, 8 Hz), 7.4 (2 H, Ph H, m), 7.5 (1 H, Ph H, m), 7.9 (2 H, Ph H, m). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.28; H, 4.65.

2-Hydroxy-2-(4-hydroxyphenyl)-1-phenylethanone (4i): white crystals, mp 186–7 °C (EtOAc/Me_2CO, 8:2) (lit. mp 173–74.5 °C,[17] 187–89 °C[9]). Because of the conflicting melting points given in the literature and the quite low solubility of **4i** in Me_2CO (the solvent used for both ^1H and ^{13}C NMR spectra),[17] we report the spectroscopic data of **4i** in order to corroborate its structure: IR (KBr) ν_{max} 3410, 1675 cm^{-1}; MS, *m/z* 155 ($M^{+\cdot}$, 3), 150 (16), 149 (15), 148 (100), 134 (26), 105 (8), 77 (13); ^1H NMR (DMSO) δ 5.8 (1 H, OH, s, D_2O exchangeable), 6.02 (1 H, CH, s), 6.72 (2 H, Ar H, d, *J* = 8 Hz), 7.24 (2 H, Ar H, d, *J* = 8 Hz), 7.45 (2 H, Ph H, m), 7.53 (1 H, Ph H, m), 7.98 (2 H, Ph H, m), 9.5 (1 H, OH, s, D_2O exchangeable).

2-Hydroxy-2-(2-hydroxyphenyl)-1-phenylethanone (4j). The crude reaction mixture was dissolved in $CHCl_3$ (30 mL). Thin-layer chromatography of the organic part indicated that dehydrocyanation of **3j** into **4j** spontaneously occurred when the solution was allowed to stand (1 week). After 1 week, the organic solution, stripped of solvent, was purified on a silica gel column (hexane/$CHCl_3$/Et_2O, 5:2.5:2.5). The last eluted fraction corresponded to **4j** (40% yield). Any attempt to convert **3** into **4** under basic conditions led to a mixture of undesired an unidentified products.

2-[4-(Dimethylamino)phenyl]-2-hydroxy-1-phenylethanone (4k): IR (KBr) ν_{max} 3410, 1675 cm^{-1}; MS, *m/z* 255 ($M^{+\cdot}$, 3) 150 (16), 149 (15), 148 (100), 134 (26), 105 (8), 77 (13); ^1H NMR ($CDCl_3$) δ 2.9 (6 H, 2 CH_3, s), 4.4 (1 H, OH, d, *J* = 6.5 Hz), 5.88 (1 H, CH, d, *J* = 6.5 Hz, s after D_2O exchange), 6.64 (2 H, Ar H, d, *J* = 8 Hz), 7.18 (2 H, Ar H, d, *J* = 8 Hz), 7.38 (2 H, Ph H, m), 7.49 (1 H, Ph H, m), 7.91 (2 H, Ph H, m).

2-(4-Bromophenyl)-2-hydroxy-1-phenylethanone (4l): IR (KBr) ν_{max} 3390, 1670 cm^{-1}; MS, *m/z* 292–290 ($M^{+\cdot}$, <1), 187–185 (M − PhCO, 8), 105 (100), 77 (40), 51 (13); ^1H NMR ($CDCl_3$) δ 4.6 (1 H, OH, d, *J* = 5.5 Hz, D_2O exchangeable), 5.92 (1 H, CH, d, *J* = 5.5 Hz, s after D_2O exchange), 7.20 (2 H, Ar H, m), 7.44 (4 H, 2 Ar H + 2 Ph H, m), 7.53 (1 H, Ph H, m), 7.9 (2 H, Ph H, m).

2-Furan-2-yl-2-hydroxy-1-phenylethanone (4o): IR (KBr) ν_{max} 3430, 1680 cm^{-1}; MS, *m/z* 202 ($M^{+\cdot}$, 15), 107 (88), 105 (100), 97 (73), 95 (16), 79 (39), 77 (55), 51 (20); ^1H NMR ($CDCl_3$) δ 4.45 (1 H, OH, d, *J* = 6 Hz, D_2O exchangeable), 6.01 (1 H, CH, d, *J* = 6 Hz, s after D_2O exchange), 6.32 (2 H, furan H, m), 7.34 (1 H, furan H, m), 7.43 (2 H, Ph H, m), 7.55 (1 H, Ph H, m), 7.94 (2 H, Ph H, m).

2-Hydroxy-2-pyridin-3-yl-1-phenylethanone (4p). The reaction was performed according to the general procedure. The solid formed was filtered off and washed with cold H_2O and then with Me_2CO. The white solid (1.50 g), recrystallized from EtOH/H_2O, melted at 216 °C dec and proved to be the hydrochloride of 1-cyano-1-phenyl-2-pyridin-3-yl-ethanediol (one isomer, 55%

(36) PhCH(OH)CN was formed in less than 5% yield. See also ref 20.
(37) Clerici, A.; Porta, O.; Arnone, A. *J. Org. Chem.* **1990**, *55*, 1240.
(38) The type of ligand at titanium determines the electronic and steric nature of the reagent. The carbonyl group is a ligand that acts as a strong π-donor. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; Chapter I.

yield): IR[40] (KBr) ν_{max} 3300–3150 (OH), 2900–2500 (NH^+); MS[39], *m/z* 213 (M – HCl – HCN, 16), 105 (100), 77 (38), 51 (7), 38–36 (HCl, 7–20), 27 (HCN, 35); ^1H NMR (DMSO) δ 5.14 (1 H, CH, s), 7.1 (1 H, OH, br, D_2O exchangeable), 7.46 (3 H, Ph H, m), 7.61 (2 H, Ph H, m), 7.8 (1 H, OH, br, D_2O exchangeable), 8.08 (1 H, dd, J = 8, 5.5 Hz, Py H meta), 8.54 (1 H, d, J = 8 Hz, Py H para), 8.82 (1 H, s, Py H ortho), 8.9 (1 H, Py H ortho, d, J = 5.5 Hz). Anal. Calcd for $C_{13}H_{13}N_2O_2Cl$: C, 58.97; H, 4.91; N, 10.58. Found: C, 58.9; H, 4.8; N, 10.6. The hydrochloride (1.0 g, 3.6 mmol) was heated under vigorous stirring in 100 mL of t-BuOH/H_2O (8:2) at 50 °C while N_2 was bubbled through the solution. When the hydrochloride was mostly dissolved, the solution was allowed to slowly cool to 25–30 °C, and then K_2CO_3 (1.0 g) was added in one portion. After 30 min. the solution was extracted with EtOAc (3 × 100 mL), washed with H_2O, dried, and evaporated. The residue was easily purified by flash column chromatography (hexane/EtOAc), 1:1). The last eluted fraction (0.72 g, 95% yield) was 2-hydroxy-2-pyridin-3-yl-1-phenylethanone, which, upon recrystallization from Et_2O, gave white crystals melting at 97–9 °C: IR (Nujol) ν_{max} 3400, 1680 cm^{-1}; MS, *m/z* 213 (4), 183 (M – CH_2O, 7), 108 (4), 107 (16), 106 (15), 105 (100), 79 (25), 78 (20), 77 (52), 51 (32); ^1H NMR ($CDCl_3$) δ 5.1 (1 H, OH, s, D_2O exchangeable), 6.05 (1 H, CH, s), 7.22 (1 H, Py H, dd, J = 8, 5 Hz), 7.42 (2 H, Ph H, m), 7.53 (1 H, Ph H, m), 7.62 (1 H, Py H para, ddd, J = 1.2, 2.2, 8 Hz), 7.90 (2 H, Ph H, m), 8.48 (1 H, Py H ortho, dd, J = 5, 1.8 Hz), 8.69 (1 H, Py H ortho d, J = 2.2 Hz). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.19; H, 5.15; N, 6.60. This product was air-sensitive and, after a few hours, was transformed into a yellow lower melting point solid which, by spectroscopic analysis, proved to be the corresponding 1-phenyl-2-pyridin-3-yl-ethanedione: mp 55 °C lit. 56–7 °C).[41]

1-Cyano-1-phenyl-2-pyridin-2-yl-1,2-ethanediol (3q) and 1-Phenyl-2-pyridin-2-yl-1,2-ethanedione. Equimolar amounts (0.01 mol) of PhC(O)CN and 2-pyridinecarboxaldehyde were allowed to react in CH_3COOH (30 mL) and aqueous $TiCl_3$ solution, according to the general procedure. After 2 h, the aqueous solution was extracted with EtOAc (3 × 200 mL). The organic layers were washed with H_2O, dried, and evaporated. The residue, upon trituration with EtOAc/Et_2O (1:1, 30 mL), afforded 1-cyano-1-phenyl-2-pyridin-2-yl-1,2-ethanediol hydrochloride (one isomer, 0.4 g, 14%): white powder, mp 193 °C dec; MS, *m/z* 108 (100), 105, 78, 77, 51, 38–36 (HCl), 27 (HCN); ^1H NMR (DMSO) δ 5.28 (1 H, CH, s), 7.5 (3 H, Ph H, m), 7.65 (2 H, Ph H, m), 7.5–8 (2 H, 2 OH, br, D_2O exchangeable), 8.02 (2 H, Py H meta, m), 8.56 (1 H, Py H para, m), 8.85 (1 H, Py H ortho, m). When the salt was dissolved in H_2O and neutralized with a K_2CO_3 solution, the free base was obtained quantitatively: white crystals, mp 118–20 °C; ^1H NMR (DMSO) δ 4.75 (1 H, CH, d, J = 6 Hz, s after D_2O exchange), 6.33 (1 H, OH; d, J = 6 Hz, D_2O exchangeable), 7.4 (4 H, 3 Ph H + Py H meta, m), 7.5 (3 H, Ph H + Py H meta, m), 7.68 (1 H, OH, s, D_2O exchangeable), 7.82 (1 H, Py H para, m), 8.49 (1 H, Py H ortho, m). The aqueous solution was added to a 30% ammonium citrate solution (20 mL) to prevent hydrolytic precipitation of TiO_2, then neutralized with a K_2CO_3 solution to pH 7–8, and extracted with EtOAc (3 × 200 mL). The organic layers were washed with H_2O, dried, and evaporated. A solution of the residual material (1.0 g) in EtOAc/Et_2O (8:2) afforded, on standing overnight, a white crystalline product (0.72 g, mp 110–18 °C), which, by ^1H NMR analysis, proved to be a mixture (1:3) of the two isomeric cyano diols (30%).[4] The more abundant isomer corresponded to the one that partially precipitated as the hydrochloride. The less abundant isomer: ^1H NMR (DMSO) δ 4.95 (1 H, CH, d, J = 6 Hz, s after D_2O exchange), 6.34 (1 H, OH, d, J = 6 Hz, D_2O exchangeable), 7.3 (7 H, 5 Ph H + 2 Py H meta, m), 7.7 (1 H, OH, s, D_2O exchangeable), 7.7 (1 H, Py H para, m), 8.27 (1 H, Py H ortho, m). Unluckily, and attempt to dehydrocyanate **3q** under basic conditions ended in failure because only the oxidation product of **4q**, 1-phenyl-2-pyridin-2-yl-1,2-ethanedione, was obtained: yellow crystals, mp 70–1 °C (lit. 72–72.5 °C)[42]; MS[43], *m/z* 211 ($M^{+\cdot}$, 16), 182 (M – CHO, m* = 156.9, 16), 155 (M – 2 CO, 7), 105 (100), 77 (62), 51 (29); ^1H NMR ($CDCl_3$) δ 7.5 (3 H, 2 Ph H + Py H, m), 7.62 (1 H, Ph H para, m), 7.95 (3 H, 2 Ph H + Py H, m), 8.2 (1 H, Py H, m) 8.65 (1 H, Py H, m).

α-Hydroxy Ketones 4r, 4s, and 4u–w. Boiling points and spectroscopic data of these compounds were consistent with the ones reported in the literature.[13]

1,3-Diphenyl-2-hydroxy-1-propanone (4t): white crystals, mp 65–6 °C (hexane/Et_2O); IR (Nujol) ν_{max} 3465, 1665, 1255 cm^{-1}; MS, *m/z* 226 ($M^{+\cdot}$, <1), 208 (M – H_2O, 47), 121 (38), 107 (97), 105 (100), 92 (74), 91 (85), 78 (55), 77 (74), 65 (15), 51 (23); ^1H NMR δ ($CDCl_3$) δ 2.88 (1 H, CH_2, dd, J = 7, 14 Hz), 3.16 (1 H, CH_2, dd, J = 4.5, 14 Hz), 3.25 (1 H, OH, s, D_2O exchangeable), 5.32 (1 H, CH, dd, J = 4.5, 7 Hz), 7.1 (2 H, Ph H, m), 7.2 (3 H, Ph H, m), 7.5 (2 H, Ph H, m), 7.62 (1 H, Ph H, m), 7.93 (2 H, Ph H, m). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.58; H, 6.20.

2-Hydroxy-1-phenyl-2-pyridin-2-yl-1-propanone (4y) and 2-Hydroxy-1-phenyl-2-pyridin-4-yl-1-propanone (4z). See ref 21.

(39) The mass spectrum of **4p** does not show the molecular ion because of the complete loss of HCN due to thermal decomposition. The presence of the CN group is confirmed by the very intense *m/z* 27 ion corresponding to $HCN^{+\cdot}$.

(40) The apparent absence of the CN group absorption is explained by its triple-bond character, which can be greatly modified by interaction with the neighboring hydroxyl groups. Raaen, V. R. *J. Org. Chem.* **1966**, *31*, 3310.

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