CYANOHYDRINS AS SUBSTRATES IN BENZOIN CONDENSATION. REGIOCONTROLLED MIXED BENZOIN CONDENSATION

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Abstract. O-Benzoylated oyanohydrins of aromatic aldehydes have been used as one of the substrates in the benzoin condensation. They were treated with aromatic aldehydes under phasetransfer conditions to result in benzoin benzoates. By this method aldehydes which fail to undergo condensation using traditional conditions could be converted into benzoins. By the Umpolung of reactivity of the pertinent aldehyde it was possible to prepare both isomeric unsymmetrical benzoins, including the thermodynamically less stable ones.

The benzoin condensation has recently been recognized as one of the general class of reactions that involve masked acyl anion equivalents as intermediates¹⁻⁵. A detailed mechanistic study⁶ showed that the active carbanion intermediate, a C-deprotonated cyanohydrin, is formed in appreciable amounts during this process (Equation 1).



Equation 1

The importance of 0-protected aldehyde cyanohydrins as masked carbonyl anion equivalents has been frequently demonstrated and is described in several reviews $^{1-5,7}$. The most systematically investigated were the trimethylsilyl ethers of aromatic and heteroaromatic aldehydes cyanohydrins^{3,8}, but other groups such as benzoyl⁹⁻¹¹, alkoxycarbonyl¹², tetrahydropyranyl^{13,14} and vinyl ether adduct^{15,16} have been used for protection of the hydroxy function. Deprotonation of these cyanohydrins under the action of strong bases, usually lithium diisopropylamide, followed by treatment with a wide variety of electrophiles is of great synthetic value. In a few cases^{8,10} alignatic aldehydes served as electrophiles giving rise to acyloins. Many improvements of the benzoin condensation have been introduced since its discovery. A traditional condensation has always been performed by heating of the aldehyde or aldehydes in aqueous alcohol as solvent with the cyanide ion as catalyst^{5,17}. The use of thiazolium salts enabled the condensation to proceed at room temperature¹⁸. It can also be performed in dipolar aprotic solvents¹⁹ or under phase-transfer conditions²⁰. Recently, ∞ -heterosubstituted benzyl phosphonate has been employed as an acyl anion equivalent in the preparation of various α -hydroxy ketones, including benzoins²¹⁻²³. Early attempts to apply 0-benzoylated aromatic aldehydes cyanohydrins as one of the substrates in benzoin condensation were reported to result in low yields of products and/or in mixtures of benzoins^{11,24}.

We report here an improvement of this method by introducing benzoates of cyanohydrines of aromatic aldehydes as one of the substrates as well as by performing this reaction in a two-phase catalytic system²⁵ (Equation 2).



Some results of our experiments are listed in Table 1.

In the first step of our procedure half of the aldehyde, or one of aldehydes in the case of mixed condensation, was converted into the cyanohydrin benzoate 1 by overnight stirring with benzoyl chloride and aqueous potassium hydroxide in the presence of phase-transfer catalyst at room temperature. In the second step, the cyanohydrin was deprotonated in a two-phase system containing 50% sodium hydroxide, and triethylbenzylammonium chloride (TEBA) and treated with the partner--aldehyde 2 to give benzoin benzoate 3. Products were purified either by orystallization or by column chromatography followed by crystallization. Hydrolysis of the masking group was achieved by treatment of 3 in acetonitrile with two molar equivalents of 0.1N sodium hydroxide at room temperature under the atmosphere of argon to provide the benzoins 4. When this reaction was carried out in the presence of air, benzoates 3 could be transformed to benzils 5 (Equation 3). Under these conditions removal of the benzoyl group from compounds possessing electronwithdrawing substituents (30, c, g) was not possible without cleavage of the central C-C bond. In the case of 3f isomerisation to the more stable isomer (4e) during hydrolysis was observed.

Using our modification of the benzoin condensation we have been able to prepare symmetrical benzoins from aldehydes which fail to undergo condensation under traditional conditions (e.g. p-nitro-, p-cyano-, p-bromo-benzaldehydes)^{5,17} as well as to control the regiospecificity of the mixed benzoin condensation. In the latter case, theoretically, two symmetrical and two unsymmetrical benzoins could be formed; in practice, only one unsymmetrical isomer is isolated. It is the thermodynamically more stable product, in which the carbonyl group is adjacent to the phenyl ring bearing the more electrondonating substituent. Our two-step procedure enables us to synthesize both of the isomeric unsymmetrical benzoins by the Umpolung of reactivity of the pertinent aldehyde. In this way we have also prepared the less stable isomers (e.g. \Im f,g) which could not be obtained by the benzoin condensation but which needed indirect methods of preparations¹⁷.

Table 1

Benzoin benzoates 3 prepared from cyanohydrins benzoates 1 and aldehydes 2 and their hydrolysis (4) and oxidation (5) products

Comp	,	OR Ar-C-CH-Ar ₁	ب م م بن ه ه ه ب ^و ف ن م ب	¥1	M.p.	ms ²	*****
	Ar	Arı	R	*	°C	Ar=C=0/+	%
<u>3</u> a	3,4-0CH ₂ 0C ₆ H ₃	3,4-0CH20C6H3	00006H5	95	167-169 ³	149	 58
<u>4a</u>	3,4-0CH20C6H3	3,4-0CH20C6H3	он	83	118-1204	149	61
<u>5</u> ª,	3,4-0CH_0C6H3	3,4-0CH20C6H3	RCH=CO	50	174 - 175 . 5 ⁵	149	100
300	4-CNC6H4	4-CNC6H4	OCOC6H5	77	123-127	130	36
<u> 2</u> 00	4-NO2C6H4	4-NO2C6H4	OCOC6H5	80	132-134	150	1
<u>3</u> d	4-BrC ₆ H ₄	4-BrC ₆ H ₄	OCOC6H5	68	106-108 ⁷	183	76
	• •	• •			9 5- 98 ⁷	185	76
<u>4</u> d	4-BrC6H4	4-BrC ₆ H ₄	OH	85	94 - 96•5 ⁸	183	76
	• •	• •				185	100
<u>5</u> d	4-BrC6H4	4-BrC ₆ H ₄	RCH=CO	57	224 - 225 ⁹	183	100
					10	185	99
<u>3</u> e	4-CH ₃ OC ₆ H ₄	с ₆ н ₅	0COC6H5	40	116-119	1 35	90
31	C ₆ H ₅	4-CH ₃ OC ₆ H ₄	0C0C6H5	72	121.5-124	105	100
<u>4</u> e	4-CH_30C6H4	C6H5	OH	82	105.5-10712	1 35	100
<u>5</u> e	4-CH_OC_H4	C6H5	RCH=CO	42	60 - 60.5 ¹³	1 35	100
<u>3</u> g	4-NO2C6H4	C6H5	ococ ₆ H5	85	141.5-143	150	3
<u>3</u> h	C ₆ H ₅	4-BrC6H4	OCOC6H5	63	130-131,5	105	100
<u>4</u> h	с ₆ н <u>5</u>	4-BrC6H4	он	64	12 6-128¹⁴	10 5	100

¹Yields are based on pure, crystalline products. ²Mass spectrometry is a very convenient tool for distinguishing between isomeric benzoins. ArC=0⁺ fragment ions appear in most of the spectra as major peaks. They accompany the predominant ester fragmentation in benzoates <u>J</u>. ³169°C²⁷. ⁴118°C²⁸. ⁵17J=174°C²⁹. ⁶One molar equivalent of 10% sodium hydroxide was used for the generation of carbanions instead of the 50% solution. ⁷Crystallizes in two polymorphic forms. ⁸58°C³⁰, 99-100°C³¹. ⁹221-223°C³². ¹⁰119.5=120.5°C³³. ¹¹127-128°C³³. ¹²89-108°C ¹⁷. ¹³61.5=65°C³⁴. ¹⁴125-126°C³².

Among experiments which were carried out we have met some exceptions. The condensation of benzaldehyde cyanohydrin benzoate with dimethylaminobenzaldehyde resulted in mixture of both benzoates 3 and their hydrolysis products 4. This may be due to the great instability of the less stable primary kinetic product rather than due to the lack of regiospecificity. Also the reactions of benzaldehyde cyanohydrin benzoate with p-nitrobenzaldehyde and p-bromobenzaldehyde cyanohydrin benzoate with benzaldehyde did not lead to a single product but to complexed mixtures of products. However, in many other cases this method gives satisfactory results (Table 1).

We have applied this modified benzoin condensation to the total synthesis of seco-isoquinoline alkaloids²⁶ with success and we believe that it will be useful in other syntheses as well.

Experimental

Melting points were determined on a Köffler block and are uncorrected. IR spectra were taken in KBr pellets on a Perkin-Elmer 180. EI mass spectra were re-corded on a Jeol MS 100D at 25 and 70eV; CI mass spectra on Finnigan 1015D spec-trometer with a model 6000 data collection system. Purity of all prepared com-pounds was checked by TLC on precoated plates (Merck, silica gel 60F 254). MN silica gel was used for column chromatography.

Cyanohydrins benzoates <u>1</u>. General procedure. Aldehyde (0.02M) was dissolved in benzoyl chloride (3ml) and dichloromethane (2ml) was added when necessary to dissolve the aldehyde. Potassium cyanide (2g) in water (6ml) was introduced dropwize at ice-bath temperature. Triethylbenzyl-ammonium chloride (TEBA, 150mg) was added and this two-phase system was stirred overnight at room temperature, and then, worked-up in the usual way. Pure products were obtained either by crystallization of the crude material from ethanol or by filtration through silica gel followed by crystallization from ethanol. filtration through silica gel followed by crystallization from ethanol.

2-Benzoyloxy-2-phenylacetonitrile.

74%. M.p. 56-59°C, $(61^{\circ}C^{35})$. Found %: C 75.84, H 4.89, N 5.69. $C_{15}H_{11}NO_2$ (237.26) req. %: C 75.94, H 4.67, N 5.90.

2-Benzoyloxy-2 (3,4-methylenedioxyphenyl) acetonitrile.

92%. M.p. 51-53°C, $(57^{\circ}C^{36})$. Found %: C 68.23, H 4.10, N 4.82; $C_{16}H_{11}NO_{4}$ (281.27) req. %: C 68.32, H 3.94, N 4.98.

2-Benzoyloxy-2(4-cyanophenyl)acetonitrile.

46%. M.p. 100-101.5°C. $P_{\text{max}} \sim 2240$, 1740. MS m/z (%): 262 (M⁺, 11) 141 (26) 105 (100) 77 (53). Found %: C 73.36, H 3.77, N 10.72; C₁₆H₁₀N₂O₂ (262.27) reg. % C 73.27, H 3.84, N 10.68.

2-Benzoyloxy-2(4-nitrophenyl) acetonitrile.

79%. M.p. $116-117.5^{\circ}C$ (dichloromethane-n-hexane). $(114-115^{\circ}C^{37})$.

2-Benzoyloxy-2(4-bromophenyl)acetonitrile.

89%. M.p. 66-67.5°C (solidified oil digested with n-hexane). \mathcal{V}_{max} cm⁻¹: 1725. MS m/z (%): 317 (M^+ , (1) 315 (M^+ , (1) 196 (1) 194 (1) 186 (17) 184 (18) 185 (26) 183 (25) 157 (12) 155 (12) 105 (100) 77 (49). Found *: C 56.80, H 3.02, N 4.31. C₁₅H₁₀NO₂Br (316.16) req. %: C 56.99, H. 3.19, N 4.43.

2-Benzoyloxy-2(4-methoxyphenyl)acetonitrile.

94%. M.p. 63-65°C (66-67°C³⁸). Found %: C 71.75, H 4.98, N 5.23. C₁₆H₁₃NO₃ (267.29) req. %: C 71.90, H 4.90, N 5.24.

Benzoin condensation. General procedure. A two-phase system composed of cyanohydrin benzoate 1 (1mM) in benzene (2-4ml), 50% sodium hydroxide (0.2ml) and triethylbenzylammonium chloride (TEBA, 15mg) was stirred for 10 min. under an atmosphere of argon. Then, the aldehyde 2 (1mM) in benzene (2-4ml) was added at ice-bath temperature and stirring was continued for 0.5-5h at room temperature. The course of the reaction was monitored by TLC. Phases were separated and the organic layer was washed with water and worked-up in the usual way.

Results of the above condensation are summarized in Table 1.

2-Benzoyloxy-1,2-bis(4-cyanophenyl)ethanone (3b).

77%. M.p. 123-127°C. \mathcal{V}_{max} cm⁻¹: 2230, 1730, 1705. CI-NH₃ MS m/z (%): 367 (M+1⁺, 34); MS m/z (%): 235 (6) 130 (26) 105 (100) 77 (46). Found %: C 75.21, H 3.96,

N 7.70. C23H14N2O3 (366.38) req. %: C 75.40, H 3.85, N 7.65.

2-Benzoyloxy-1,2-bis(4-nitrophenyl)ethanone (3c).

80%, M.p. $132-134^{\circ}$ C. \mathcal{V}_{max} cm⁻¹: 1720, 1700. CI-NH₃ MS m/z (%): 407 (M+1⁺,3). MS m/z (%): 255 (1) 150 (6) 135 (20) 105 (100) 77 (33). Found %: 62.34, H 3.43, N 6.76. C₂₁H₁₄N₂O₇ (406.36) req. %: C 62.07, H 3.47, N 6.89.

2-Benzoyloxy-1,2-bis(4-bromophenyl)ethanone (3d).

68%. M.p. 106-108°C or 95-98°C (polymorphism). μ_{max} cm⁻¹: 1715, 1690. MS m/z (%): 475 (M⁺, (1) 291 (42) 289 (45) 185 (77) 183 (79) 105 (100) 77 (100). Found X: C 53.57, H 2.92, C₂₁H₁₄0₃Br₂ (474.15)req. %: C 53.20, H 2.98.

2-Benzoyloxy-1(4-nitrophenyl)-2-phenylethanone (3g).

85%. M.p. 141.5-143°C (methanol). P_{max} cm⁻¹: 1720, 1690. MS m/z (%): 257 (2) 150 (3) 135 (30) 105 (100) 77 (55). Found %: C 69.50, H 4.38, N 3.71. C₂₁H₁₅NO₅ (361.36) req. %: C 69.80, H 4.18, N 3.88.

2-Benzoyloxy-2 (4-bromophenyl)-1-phenylethanone (3h).

63%. M.p. 130-131.5°C. \mathcal{P}_{max} cm⁻¹: 1705, 1680, MS m/z (%): 396 (2) 394 (2) 291(10) 289 (10) 105 (100) 77 ($3\overline{2}$). Found %: C 63.59, H 3.89; C₂₁H₁₅BrO₃ (395.26) req. %: C 63.81, H 3.83.

Hydrolysis of benzoyl group. General procedure. Benzoin benzoate 3 (1mM) was dissolved in acetonitrile (50ml) and argon was bubbled for 15 min. 0. TN Sodium hydroxide (2mM, 20ml) was then added dropwize (ca. 0.5h) and the solution was stirred at room temperature until TLC indicated no more starting benzoate. The reaction mixture was then acidified with 5% hydro-chloric acid and acetonitrile was removed under reduced pressure. The aqueous re-sidue was extracted with ether and the organic extracts were washed with 5% sodium hydroxide and with water, and then worked-up in the usual way. The prepared benzoing 4 are characterized in Table 1. The prepared benzoins 4 are characterized in Table 1.

Hydrolysis and air oxidation of benzoin benzoates 3. General procedure. A solution of benzoin benzoate 3 (1mM) in acetonitrile (50ml) and 0.1N so-dium hydroxide (2mM, 20ml) was stirred at room temperature until TLC indicated the disappearance of alower moving compound (benzoin), formed as intermediate product. The reaction mixture was then acidified with 5% hydrochloric acid and worked-up as above.

The prepared benzils 5 are characterized in Table 1.

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