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OXIDATIVE BENZOIN REACTIONS

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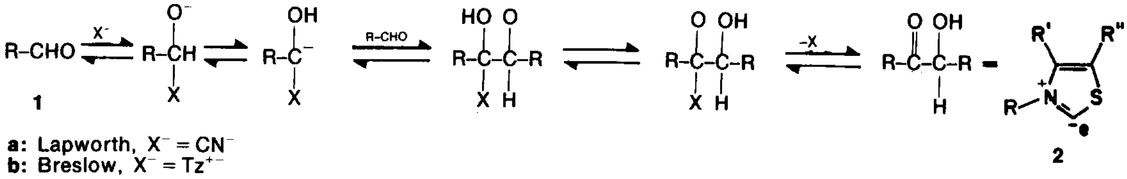
Abstract—A one-pot synthesis (yields over 50%) of methyl and ethyl esters from aldehydes (and the corresponding alcohol), using aromatic nitrocompounds as oxidizing agents under the catalytic action of cyanide ion or of a conjugate base of a thiazolium ion, is described. A variety of by-products (α-hydroxybenzylidenaniline (**16**), α-methoxybenzylidenaniline (**21**), α-cyanobenzylidenaniline (**27**), N^1-hydroxy-N^1,N^2-diphenylbenzamidine (**28**), and others) have been identified.

The role of cyanide ion in the benzoin condensation was explained many years ago by Lapworth,[1] who proposed a reaction mechanism which, in its more fundamental aspects, has been recently confirmed by Kuebrich *et al.*[2] (Scheme 1, $X^- = CN^-$). Lapworth's mechanism has been adapted to explain processes closely related to the benzoin condensation.[3]

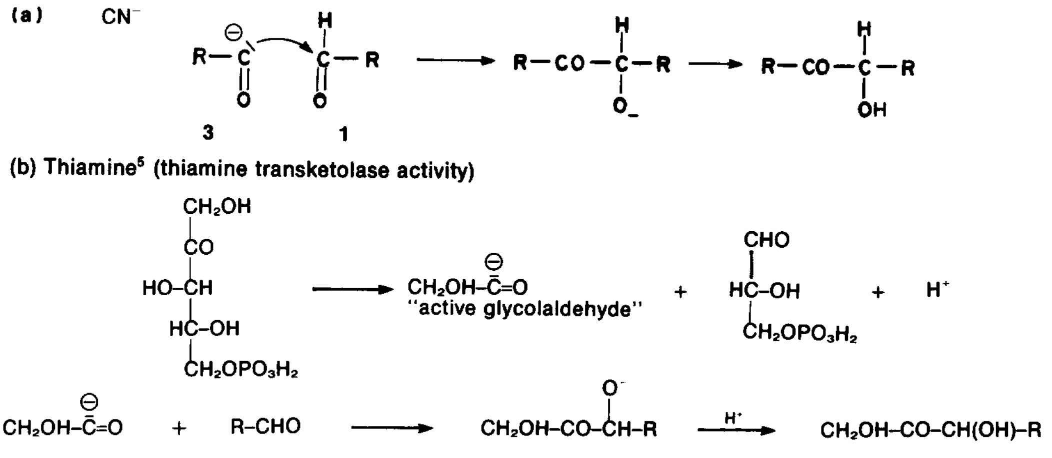
In 1958, Breslow, in a now classical paper,[4] explained the biochemical activity of thiamine diphosphate by showing that the conjugate bases of thiazolium ions (Tz^{+-}) catalyzed the benzoin condensation in much the same way as cyanide ion does (Scheme 1, $X^- = Tz^{+-}$).

The key features in the mechanism of the benzoin condensation are the stabilized carbanions (**2**) which, in modern organic chemical parlance, are masked CO groups with inverted reactivity and, in a biochemical context, are the "active aldehydes" which appear, among others, in the several chemical transformations for which thiamine serves as a cofactor. In an oversimplified formulation, it can be said that, through the agency of a cyanide ion or of a conjugate base of thiazolium ion, the aldehyde behaves as a nucleophile formally depictable as an acyl anion $R-\overset{\ominus}{\bar{C}}=O$ (**3**) (Scheme 2).

After Breslow's paper, the similiarity of catalytic effects of the cyanide ion and the conjugate bases Tz^{+-} was generally accepted and served as a guide in future chemical work but, for many years, this work was limited to the field of the benzoin condensation and closely related processes. Thus, it was demonstrated, soon after Breslow's paper, that cyanide ion, as well as thiamine, catalyzes decarboxylation of α-oxocarboxylic acids[6]; rather surprisingly, kinetic support of Breslow's suggestion has not been presented until very recently[7]. Babicheva *et al.*[8] have modified or, better, have com-



Scheme 1.



Scheme 2.

plemented Lapworth's mechanism by introducing radical species, which they detected by EPR. The presence of radicals would explain oxygen and peroxide effects on the course of benzoin condensations, especially in those performed under Tz^{+-} catalysis. The heuristic value of considering Lapworth's (**3a**) and Breslow's (**3b**) intermediates as masked aldehydes with inverted reactivity, which could be used in reactions other than benzoin condensations, seem to have not been fully appreciated until recently. In this context, Stetter's work on Michael type reactions,[9,10] that is to say, the addition of aldehydes to activated double bonds, deserves special mention. Apparently, Nature makes no use of this capability of Breslow's intermediates to take part as addends in Michael condensations.

The present paper deals with reactions in which, using nitro compounds as coreagents, aldehydes are converted directly into acid derivatives. The key feature of these reactions is an oxidation of a Lapworth's or a Breslow's intermediate, what justifies our naming them "oxidative benzoin reactions". Two preliminary communications on the subject have appeared.[11,12] At a biochemical level, "oxidative benzoin reactions" are rather common, but purely chemical related work is scarce. To our knowledge, it can be summarized as follows: (a) Analytical reduction of 1,2-dinitrobenzene to 2-nitrophenylhydroxylamine by aldehydes, in the presence of cyanide ion.[13] (b) Cyanide catalyzed manganese dioxide oxidation of aldehydes[14] and related groups.[15] (c) Tz^{+-} catalyzed quinone oxidation of aldehydes.[16] (d) Micellar catalysis of flavin oxidation of aldehydes, assisted either by cyanide ion[17] or by a conjugate base of thiazolium ion.[18]

To the above references, a patent[19] claiming that carbonyl compounds, including aldehydes, may be oxidized to the corresponding carboxy compounds, using a thiazolium compound or cyanide ions as catalyst for the oxidation, must be added.

Oxidative benzoin reactions with nitro compounds as oxidizing agents

The starting point of our work was a, at the time, rather unexpected result which we found in an attempted benzoin condensation of 4-nitrobenzaldehyde, using the conjugate base of 3,4,5-trimethylthiazolium ion as catalyst. Working in DMF we could isolate 4-nitrobenzoic acid and, in methanol, methyl 4-nitrobenzoate was obtained in a rather substantial yield (62%); in this operation, dimethyl axoxybenzoate and dimethyl azobenzoate were identified as well. We soon realized that this result was not surprising because when nitrobenzaldehydes are used as substrates in cyanide catalyzed benzoin condensations, "anomalous" results are also found[20–28]; as a matter of fact, long ago, these reactions were the subject of a bitter controversy between two research teams (led by Popovici and Ekecrantz). A critical analysis of the literature on this subject, carried out in the light of our own results, allows to summarize the situation on the following way: (a) Aromatic nitro aldehydes do not give rise, under the catalytic action of cyanide ion or the conjugate bases of thiazolium ions, to observable benzoin condensations; instead, a self oxido-reduction, catalyzed also by cyanide ion or Tz^{+-}, takes place. Undoubtedly, benzoin condensation does occur, but its reversible nature makes it unobservable if a competing irreversible process (the oxido-reduction reaction) takes place simultaneously. (b) The aldehyde group is oxidized to the carboxylic group level. Depending on working conditions, an acid or an acid derivative is obtained. (c) Reduction of the nitro group occurs in a manner highly dependent on the particular reaction and reaction conditions, a fact which is not surprising in view of the variety of oxidation states that nitrogen derivatives can exhibit and of the reactions in which these derivatives can take part. A few examples will illustrate the above assertions:

(i) In attempted benzoin condensations of 2-nitrobenzaldehyde, 2-nitrobenzoic acid[22] and 2-azoxybenzoic acid[20,22] were isolated.

(ii) Starting from 4-nitrobenzaldehyde, 4-nitrobenzoic acid was identified.[20]

(iii) When the cyanohydrin of 4-nitrobenzaldehyde is treated with diluted alkaline solution, 4-nitrobenzoic, 4-azobenzoic and 4-nitrosobenzoic acids could be isolated.[25]

(iv) Dimethyl azobenzoate and dimethyl azoxybenzoate were isolated in the reactions of nitrobenzaldehydes with quinazoline, in presence of methanol.[3] Once the operation of self oxido-reduction reaction in which under the catalytic action of cyanide ion or of a conjugate base Tz^{+-}, a nitro group is reduced and an aldehyde group is oxidized, has been established, the way is logically open to study the feasibility of oxidizing aldehydes into acid derivatives by means of nitrobenzene or any other nitro derivative. However, before our entry in the field, this feasibility had not been explored.

Presentation of the work done. We have centered our interest in the oxidation of aldehydes by nitrocompounds, *in presence of alcohols*; in these circumstances, the main oxidation product should be, in principle, the corresponding ester, which means that the reaction represents a potential "one-pot" procedure for direct conversion of aldehydes into esters.

Throughout the numerous experiments which were performed, two main goals were in mind: (a) Establishment of working conditions that would make a convenient synthetic procedure of the oxidative benzoin reaction; (b) A knowledge as complete as possible of by-products present in reaction mixtures, in order to clarify our views on the reaction mechanism.

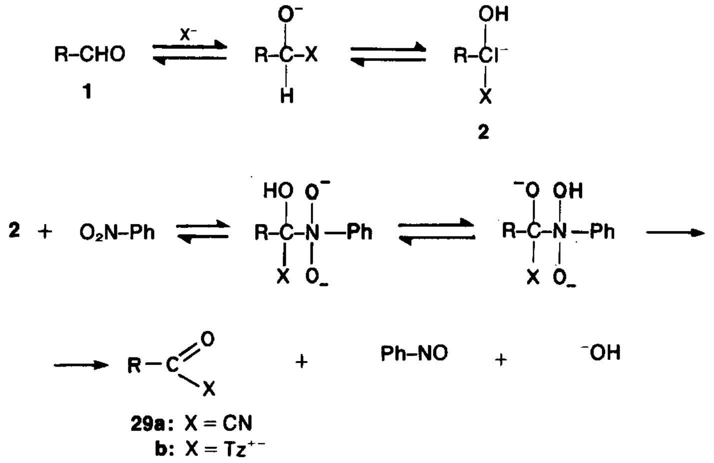
The reaction was carried out using as catalysts: (a) Conventional thiazolium salts, in the presence of base (to generate the conjugate bases); (b) Insoluble polymer-supported thiazolium salts, in the presence of base; (c) Potassium cyanide.

Cyanide catalyzed reactions have been the ones which we have studied more carefully, reactions being performed according to three general types of working procedures: In type I procedures a large excess of alcohol is used, in such a way that the alcohol acts both as the reagent and as the solvent for potassium cyanide; in type II and III procedures, alcohol is used only as reagent, in a reaction medium such as benzene, in which potassium cyanide is dissolved either with assistance of a crown-ether (type II) or of a quaternary ammonium salt (type III).

The highest yields in ester attainable by type I and II procedures are rather similar, but in benzene, in presence of a crown-ether, reactions are faster and cleaner and yields in isolable by products are increased substantially. As a rule, the whole amount of identified oxidation products (including the ester) which can be isolated, sums up to 70–75%.

Type III procedures, in which a quaternary ammonium salt is used as phase transfer catalyst, have proved unsatisfactory. This fact can be related to published results[29] according to which crown-ethers are about a hundred times more efficient than quaternary ammonium salts in solid-liquid phase transfer catalysis of cyanide ion.

A mechanism for the first steps of the oxidative benzoin reaction, based on the acceptance of Lapworth's mechanism for the benzoin condensation and on strict analogy between a CO and NO_2 group, would be the one depicted in Scheme 3.



Scheme 3.

However, N in a NO_2 group is known to be a poorer electrophilic center than C in a CO group; for example, a NO_2 group hardly exchanges its oxygens when treated with H_2 ^{18}O in either acidic or alkaline media[30]. On the other hand, as it has been pointed out before, Babicheva *et al.* have complemented Lapworth's mechanism by introducing radical steps into the accepted scheme and work in our own laboratories[31] confirm the presence of radical species in oxidative benzoin reactions. In fact, when benzaldehyde is added to a methanol solution of nitrobenzene and potassium cyanide, a strong EPR spectrum, assignable to nitrobenzene radical-anion[32], can be registered. Methanol solutions of nitrobenzene, 4,5-diphenyl-3-methylthiazolium iodide, benzaldehyde (or furfural), and ethyl-diisopropylamine, give rise to a complex spectrum, in which the signals from nitrobenzene radical-anion can also be identified.

Tentative proposal. Tentatively, the following radical mechanism is suggested for the initial steps of oxidative benzoin reactions (Scheme 4).

Other comments. Through similar ionic or radical mechanisms to those given, nitrosobenzene can oxidize more Lapworth's intermediate, affording again acyl cyanide, **29a** or 2-acylthiazolium ion, **29b**, and the corresponding reduction product, which now is phenylhydroxylamine; for the sake of simplicity, the ionic mechanism is illustrated (Scheme 5).

The important point to remark here is that, be it through an ionic or through a radical mechanism, we accept that acyl cyanide or 2-acylthiazolium ion, nitrosobenzene and phenylhydroxylamine are formed as reaction intermediates and that they enter into further reactions which lead to the observed products and by-

Table 1. Oxidative benzoin reactions. Catalyst: conventional thiazolium salts, using triethylamine as a base

RUN	1	2	3	4	5	6	7	8	9
R-CHO (1) MOLAR PROPORTION	1a 1	1b 1	1b 1	1b 1	1b 1	1b 1	1c 1	1c 1	1c 1
R-OH (4) MOLAR PROPORTION	4a 25	4a 20	4a 16	4a 20	4c 20	4e 1	---	4a 58	--
Nitrobenzene MOLAR PROPORTION	1	1	1	1	1	1	--	--	1
Thiazolium salt MOLAR PROPORTION	5a 0.1	5b 0.1	5a 0.1	5c 0.2	5a 0.1	5a 0.1	5a 0.05	5a 0.05	5a 0.1
Triethylamine MOLAR PROPORTION	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	--
Solvent MOLAR PROPORTION	4a 25	4a 20	4a 16	4a 20	4c 20	6 8	7 30	4a 58	8 7
Reaction time HOURS	264	96	72	96	216	48	20	120	96
Reaction temperature °C	65	60	60	60	80	80	75	70	70
Ester molar yield %	59	79	65	51	23	42	70*	62	84†
Other products	8,9	9,10	9,10	9,10	11	11,12	--	13,14	--

*The reaction product was 4-nitrobenzoic acid

†The reaction product was N-(4-aminobenzhydril)-aniline

Table 2. Oxidative benzoin reactions. Catalyst: potassium cyanide

RUN	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
R-CHO (1) MOLAR PROPORTION	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1a 1	1d 1	1e 1
R-OH (4) MOLAR PROPORTION	4a 13	4a* 25	4a 19	4a 50	4a* 50	4a 50	4a* 50	4a* 50	4a* 50	4a 50	4a 36	4a 50	4a 50	4a 50	4a 50	4a* 50	4a* 50	4a* 50	4b* 36	4a 13	4a 20	4a 20	4c 13	4c 13	4a 33	4a 20
R-NO_2 (15) MOLAR PROPORTION	15a 2	15a 1	15b 2	15b 2	15b 1	15c 2	15c 1	15c 1	15c 1	15d 2	15d 2	15d 2	15d 1	15d 1	15d 1	15d 1	15d 1	15d 1	15d 1	15e 1,5	15f 2	15f 1	15a 1	15a 1	15a 1	15a 0,5
KCN MOLAR PROPORTION	0.08	0.1	0.03	0.1	0.1	0.4	0.4	0.1	0.2	0.4	0.12	0.12	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.08	0.08	0.08	0.1	0.1	0.1	0.4
Solvent MOLAR PROPORTION	4a 13	4a 25	4a 19	4a 50	4a 50	4a 50	4a 50	4a 50	4a 50	4a 50	4a 36	4a 50	4a 50	4a 50	4a 50	4a 50	4a 50	4a 50	4b 36	4a 13	4a 20	4a 20	4c 13	4c 13	4a 33	4a 20
Reaction time HOURS	22	92	45	28	90	28	22	90	8	18	30	0.5	1.5	5	7	7	8.5	90	8.5	33	20	22	24	72	72	18
Reaction temp. °C	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	78.5	65	65	65	82	82	65	65
Ester molar yield %	54	44	37	65	28	42	9	30	30	17	40	6	4	14	18	28	32	8	32	0	0	0	tr.	tr.	9.3	38.5
Other products %		9 8							16b 11		18 30	18 12								18 4			19 12	19 24	16c 3.3	20 19
		16a 14.4							17 1.2														20 9	20 9.2		21b 18.3

*Absolute alcohol was used.

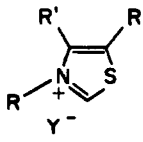
Table 3. Oxidative benzoin reactions. Catalyst: potassium cyanide with phase transfer catalysts

RUN	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
R-CHO (1) MOLAR PROPORTION	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1a *1*	1e *1*	1a *1*	1a *1*	1a *1*
R-OH (4) MOLAR PROPORTION	4a *1*	4a *1*	4a *1*	4c *1*	4a *1*	4a *1*	4a *1*	4c *1*	4d *3*	4a *1*	4a *1*	4a *1*	4a *8*	4a *1*	4c *1*	4c *4*	4d *4*
Nitrobenzene MOLAR PROPORTION	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	*1*	*0.5*	*0.5*	*0.5*	*0.5*	*0.5*	*0.5*	*0.5*
Potassium cyanide MOLAR PROPORTION	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	*0.1*	*0.4*	*0.4*	*0.4*	*0.4*	*0.4*	*0.4*	*0.4*	*0.4*
Phase Trans. Cat. MOLAR PROPORTION	22 *0.1*	22 *0.1*	22 *0.2*	22 *0.2*	23 *0.1*	23 *0.1*	23 *0.1*	23 *0.1*	23 *0.05*	24 *0.03*	24 *0.03*	24 *0.03*	24 *0.03*	24 *0.03*	24 *0.03*	24 *0.03*	24 *0.03*
Solvent MOLAR PROPORTION	25 *7*	--	--	--	25 *4.5*	26 *5*	--	--	4d *3*	25 *4*	25 *4*	25 *4*	4a *8*	25 *4.5*	25 *4*	4c *4*	4d *4*
Reaction time HOURS	*24*	*24*	*24*	*24*	*24*	*60*	*48*	*96*	*24*	*24*	*8*	*8*	*8*	*14*	*14*	*14*	*22*
Reaction temper. °C	*80*	*80*	*80*	*80*	*80*	*101*	*80*	*80*	*82*	*80*	*80*	*80*	*65*	*80*	*80*	*82*	*room*
Ester molar yield %	*0*	*27*	*30*	*0*	*0*	*0*	*28*	*tr*	*0*	*36*	*47*	*46*	*52*	*44.4*	*2.5*	*8*	*0*
Other products m.y. %		21a *6*		19 *58*				19 *52*	19 *48*	27a *tr*	20 *19.3*	20 *22*	20 *18.6*	20 *30*	20 *27.9*	20 *28.4*	20 *18.8*
				16a *1*				20 *6*	20 *3*	21a *tr*	27a *4.6*	27a *tr*	27a *1.2*	27b *2.5*	27a *7.15*	19 *30*	27a *5*
											21a *tr*	21a *tr*	21a *1.5*	16d *1.2*	16a *tr*		19 *25.3*
											16a *5.4*		16a *1.6*		19 *35.3*		
											28 *2*						

1a: R = Ph
b: R = 2-furyl
c: R = 4-NO_2-Ph
d: R = 4-CH_3O-Ph
e: R = 4-Cl-Ph

4a: R = CH_3
b: R = C_2H_5
c: R = i-C_3H_7
d: R = t-C_4H_9
e: R = $C_{18}H_{37}$

5



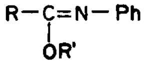
a: R = R' = R'' = CH_3, Y = I
b: R = $PhCH_2$, R' = CH_3, R'' = H, Y = Cl
c: R = CH_3, R' = R'' = Ph, Y = I

6: 1,2-dimethoxyethane
7: N,N-dimethylformamide
8: aniline
9: azoxybenzene
10: azobenzene
11: 2-furoic acid anilide
12: furil
13: dimethyl azoxybenzoate
14: dimethyl azobenzoate

15a: R = Ph
b: R = 2-CH_3-Ph
c: R = 4-CH_3-Ph
d: R = 1-naphtyl
e: R = CH_3
f: R = 3-NO_2Ph

16 R-CONHPh **a**: R = Ph
b: N-(4-tolyl)-benzamide
c: R = 4-CH_3O-Ph
d: R = 4-Cl-Ph

17: methyl mandelate
18: benzaldehyde dimethylketal
19: benzoin benzoate
20: potassium benzoate
21



$R{-}\underset{OR'}{C}{=}N{-}Ph$

a: R = Ph, R' = CH_3
b: R = 4-Cl-Ph, R' = CH_3

22: Triethylbenzylammonium chloride
23: Trioctylmethylammonium Chloride
24: dibenzo-18-crown-6-ether
25: benzene
26: 1,4-dioxane
27: R—C(CN)=N—Ph **a**: R = Ph
b: R = 4-Cl-Ph

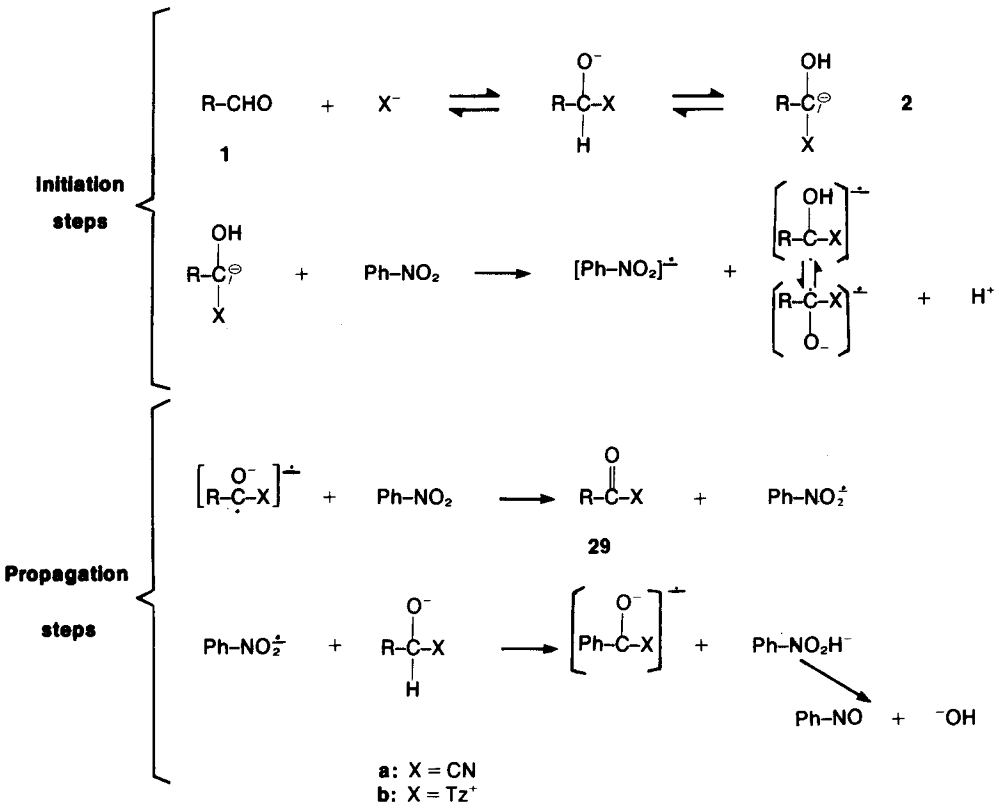
28: N^1-hydroxy-N^1, N^2-diphenylbenzamidine

products. Particularly, as a whole family of by-products can be interpreted as having nitrone, **30**, as the common precursor (see below), it seems reasonable to accept that nitrone, **30**, is formed by reaction between the starting aldehyde and phenylhydroxylamine (Scheme 6).

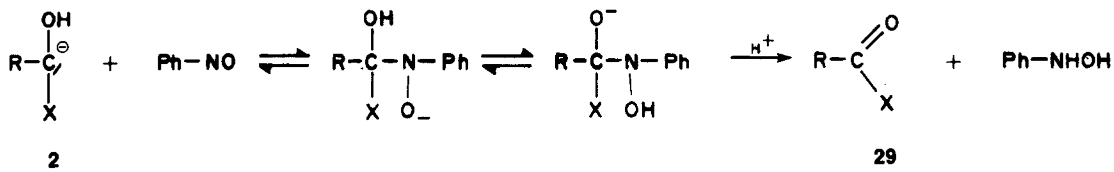
However, it must be pointed out here that we have not been able to identify nitrone, **30**, in any of the numerous reaction mixtures which we have analyzed. It is worth mentioning that, implicity or explicity, any interpretation of the reaction under study must admit that normal benzoin condensation occurs simultaneously and that, in any case, if the corresponding benzoins are not observed it is only because this reversible reaction cannot compete successfully with irreversible processes.

Disappearance of cyanide ion by formation of Meisenheimer complex between this ion and 1,3-dinitrobenzene[33] can account for the failure of the reaction when this nitro compound was used as oxidizing agent.

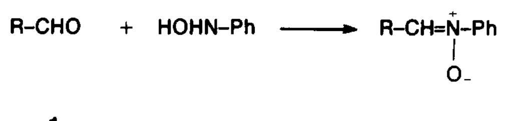
Besides Meisenheimer complex formation, several possible alternative reactions of cyanide ion can be responsible for the variable yields of ester reported in the Tables: (a) Oxidation of cyanide to cyanate by nitro



Scheme 4.



Scheme 5.



Scheme 6.

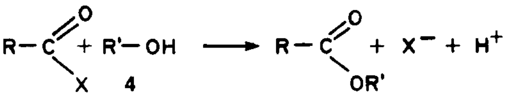
compounds;[34] (b) Aromatic nucleophilic substitution of a NO_2 group by a CN group; (c) Formation of mandelonitrile and subsequent alcoholysis of this compound; (d) Von Richter reactions between nitro compounds and cyanide ions.[35]

Thiazolium salts are far more unstable than cyanide ion under the conditions which prevail in oxidative benzoin reactions. This is clearly put forward by the fact that polymer-supported thiazolium salts can be re-used several times when they are employed in benzoin condensations,[36] while they can be used only once if they are employed in oxidative benzoin reactions.

Acyl cyanide, **29a**, *and 2-acylthiazolium ion,* **29b**, *reactions.* The acyl cyanide which we suppose is formed in the initial stages of the reaction, when cyanide ion is used as catalyst, is very reactive towards nucleophiles present in the reaction medium and, consequently, a variety of reactions can take place. The same can be said[37] of the acylthiazolium cation formed in the case a conjugate base Tz^{+-} is used.

(i) *Ester formation*

If a primary alcohol such as methanol or ethanol is used, its high nucleophilicity ensures that the main reaction is the formation of the corresponding ester:



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This is, of course, the basis of the *preparative reaction*, examples of which are given in runs 1 to 6, 9 to 31, 34 to 38, 40 to 42 and 45 to 49. Yields higher than 50% can be obtained with no difficulty.

(ii) *Potassium salt formation*

Formation of the corresponding potassium salt had been observed in several runs, but a systematic quantification of the amount of salt formed was done only from run 43 on (Table 3), that is to say, in runs carried on in the presence of crown-ether. Yields in isolated acids were between 20 and 30% and we think that, most probably, the K salt was formed in similar amounts in all runs.

The salt must be formed in the reaction of acyl cyanide either with hydroxyde ion the presence of which can be justified by the proposed mechanism:

$$R{-}CHO + O_2N{-}Ph + CN^- \rightarrow R{-}COCN + PhNO + {}^-OH$$

or with water, the presence of which (even using dry reagents) can be justified by the stoichiometry of the complete reaction:

$$R{-}CHO + O_2N{-}Ph + R'{-}OH \rightarrow R{-}COOR' + Ph{-}NO + H_2O$$

(iii) *Benzoin benzoate formation*

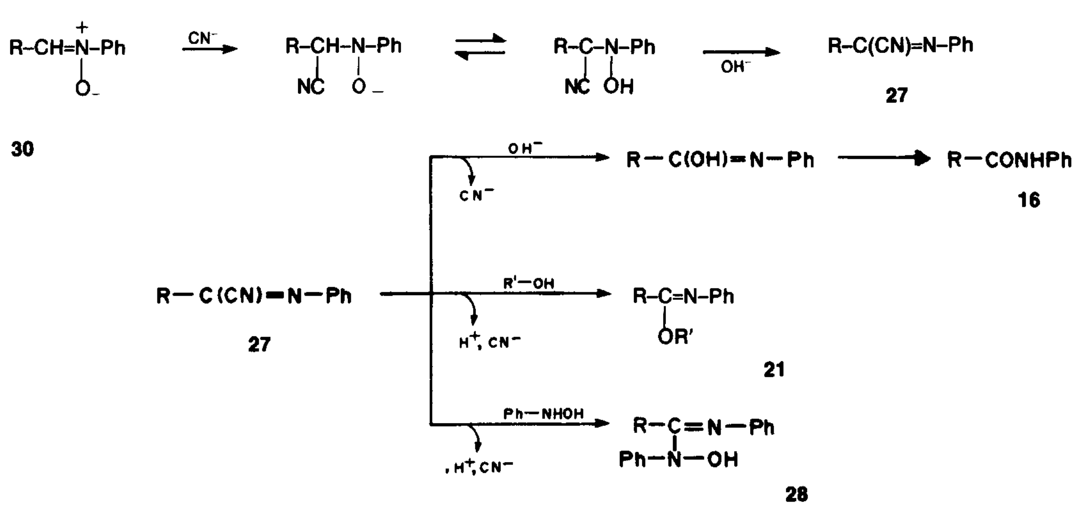
As already pointed out, benzoin should be omnipresent in our reaction mixtures and, consequently, there is always an open possibility of its acting successfully as a competitive nucleophile towards acyl cyanide (or acylthiazolium ion). In fact, this is what we admit that happens when isopropanol and t-butanol, that have a lower nucleophilicity than methanol and ethanol, are used as reagents, under a variety of conditions. In these experiments (runs 32, 33, 39, 43, 44, 50, 51, 52), benzoin benzoate is isolated in yields as high as 58%. In order to gather support for our mechanistic interpretation, benzoyl cyanide was prepared independently and its reactions with several alcohols were studied (Table 4). As can be observed, if isopropanol is the *only* available nucleophile, isopropyl benzoate is obtained in high yield, but with equimolar mixtures of isopropanol and benzoin, the latter is the successful nucleophile. Almost quantitative formation of benzoic acid, in the high temperature (110°C) reaction between benzoyl cyanide and t-butanol, is in line with the low nucleophilicity of this alcohol and its decomposition into isobutene and water (Table 4).

By-products related to nitrone. Careful analyses of oxidative benzoin reaction mixtures, carried out after removing excess reagents and ester formed as the main product, have led to the identification of a variety of by-products which can be traced back to a common precursor, the nitrone, **30**. Scheme 7, based on Bellavita's previous work,[38] summarizes reasonable mechanistic pathways: α-methoxybenzylidenaniline (**21**), N^1-hydroxy-N^1,N^2-diphenylbenzamidine (**28**), and α-hydroxybenzylidenaniline (**16**) (immediately tautomerized to benzanilide) would be formed from the pertinent nucleophile and α-cyanobenzylidenaniline (**27**), and this derivative itself would be formed directly from the nitrone (**30**), by reaction with cyanide ion.

The alternative formation of the key cyanoderivative (**27**) by reaction between benzoyl cyanide and aniline (a reaction product of nitrobenzene, that has been identified

Table 4. Reaction between benzoyl cyanide and several alcohols

ALCOHOL	REACTION PRODUCT	%	TEMPERATURE /°C
Methanol	Methyl benzoate	93	65
Isopropanol	Isopropyl benzoate	83	90
Benzoin	Benzoin benzoate	70	65
Benzoin 1:1 Isopropanol	Benzoin benzoate Isopropyl benzoate	50 traces	room temp.
t-butanol	Benzoic acid	98	110
t-butanol	No reaction		room temp.



Scheme 7.

in some experiments) seems less probable. α-Methoxybenzylidenaniline is quantitatively hydrolyzed to benzanilide under acid catalysis; a clean working procedure is simple passage through a silica-gel column.

Other by-products. As the presence in the reaction mixture of small amounts of any of possible reduction products of nitrobenzene, was to be expected, no systematic efforts were devoted to confirming it. However as Table 1 shows, aniline, azobenzene and azoxybenzene were isolated in some experiments.

In a case, a small amount (1.4% yield) of methyl mandelate was obtained. The presence of this ester can be explained by methanolysis of mandelonitrile, that is to say, of the cyanohydrin of benzaldehyde.

EXPERIMENTAL

M.ps were taken in capilary tubes and are uncorrected. IR spectra were recorded on a Pye Unicam SP 1100 Infrared Spectrophotometer, NMR spectra on a Perkin–Elmer R-12 (60 MHz) spectrometer using TMS as internal standard and Mass spectra on a Hewlett-Packard 5700-A spectrometer.

Oxidative benzoin reactions, using conventional thiazolium salts as catalyst

All reactions (runs 1–9) were carried out under the same experimental conditions. In a 3-necked round bottomed flask equipped with a reflux condenser and argon or N_2 input, a mixture of aldehyde, nitrobenzene, (in runs 7 and 8 no nitrobenzene was used), thiazolium salt and Et_3N were solved in MeOH, which was used both as a reagent and as a solvent. The mixtures were kept at 60–80° for the specified time (Table 1) and then treated with CH_2Cl_2 and cold water; the organic layers were washed, dried over Na_2SO_4 and evaporated under reduced pressure. The crude products were distilled and the residues were studied by column chromatography on silica-gel. The products were characterized by comparison with authentic samples synthesized at the same time. Yields are based on NMR spectrum integrations.

A typical operation (run 2) used 5.79 g of furfural, 7.43 g of nitrobenzene, 1.54 g of 3,4,5-trimethylthiazolium iodide and 1.8 ml of triethylamine in 50 ml MeOH. After treatment, 5,993 g methyl furoate was obtained, by distillation, and 0,357 g of azobenzene (**10**) and 1,415 g of azoxybenzene (**9**), by column chromatography (CCl_4).

Oxidative benzoin reactions, using potassium cyanide as catalyst

(Experimental conditions were similar to those employed with the conjugate bases of thiazolium ions).

Reaction using methanol (*run* 11). A mixture prepared from 5.30 g benzaldehyde, 6,16 g nitrobenzene, 0,325 g KCN and 50 ml MeOH, was kept refluxing, during 92 hr, under argon. The mixture was then treated with CH_2Cl_2 and water. The organic layer was washed until neutral pH, dried and evaporated. The residue was distilled under reduced pressure yielding 7,414 g of a mixture of benzaldehyde, nitrobenzene and methyl benzoate. The yield (NMR monitoring) in oxidation product was 44%. The undistilled residue was treated with 2 N HCl, the aqueous layer was neutralized with 5% NaOH and extracted, with CH_2Cl_2. The organic layer was dried and evaporated, obtaining 0.1 g of **8**. The residue was column chromatographed on silica-gel, collecting 245 fractions of 30 ml. The following products were identified: azoxybenzene (**9**), 0,256 g (hexane/CH_2Cl_2 7:3), methyl benzoate, 0.123 g (hexane/CH_2Cl_2 7:3) and benzanilide (**16a**), 1.336 g, m.p. 162–163° (from MeOH) (lit.[39] 163°) (hexane/CH_2Cl_2 1:1).

Reaction using isopropanol (*run* 33). Under N_2, 2.65 g purified benzaldehyde[40], 3.08 g nitrobenzene (freshly distilled), 0.163 g KCN and 25 ml i-PrOH (dried over LAH), were mixed with magnetic stirring. The reaction was refluxed for 72 hr. A white solid was formed which was recovered by suction filtration, washed with ether and dried, affording 0.359 g of **20**, m.p. over 250°. The filtrate was cooled in the refrigerator, giving 0.616 g of a crystalline white solid, which was removed by suction filtration and washed with cold MeOH. This solid showed m.p. 123–124° (from EtOH) and was identified as benzoin benzoate, (lit.[41] 124–125°). IR (KBr) ν_{max}: 2960, 1715 (ester), 1695 (ketone) cm^{-1}; NMR ($DCCl_3$) δ: 7,1 (s, 1H, CH), 7,2–8,3 (m, 15H, ArH); MS *m/e*: 316 (M$^+$) (3%), 211 (76), 106 (42), 105 (100), 77 (87). Basic hydrolysis afforded benzoin and sodium benzoate.

The filtrate was evaporated under reduced pressure and the NMR spectrum of the crude residue revealed only the presence of traces of isopropyl benzoate.

Oxidative benzoin reactions, using potassium cyanide in presence of a phase transfer catalyst

(All reactions (Table 3) were performed in a 50 ml round bottomed flask with magnetic stirring and under N_2; previously the mixtures had been carefully deoxygenated).

When dibenzo-18-crown-6-ether was used as phase transfer catalyst, the aldehyde was added after the mixture of nitrobenzene, KCN, crown ether and solvent, had been stirred, for 30 min.[42]

Reaction using methanol and triethylbenzylammonium chloride (*run* 37). A mixture of 2.65 g benzaldehyde, 3.08 g nitrobenzene, 0.568 g triethylbenzylammonium chloride, 0.163 g KCN and 0.8 g MeOH, was held at 80° for 24 hr. Then, it was treated with water, to remove the catalyst, and extracted with CH_2Cl_2. The organic layer was washed, dried, evaporated and the residue was distilled under reduced pressure. Methyl benzoate, nitrobenzene and **21**, were identified (NMR analysis) in the distilled product.

Reaction using isopropanol and triethylbenzylammonium chloride (*run* 39). A mixture of 2.65 g benzaldehyde, 3.08 g nitrobenzene, 1.336 g triethylbenzylammonium chloride, 0.163 g KCN and 1.5 g i-PrOH was held at 80° for 24 hr. NMR monitoring showed total reaction of benzaldehyde, but no formation of the expected ester. The crude mixture was cooled in the refrigerator and a solid was formed, which as removed by suction filtration, washed with cold MeOH and dried. The crystalline white solid, m.p. 123–124° (from EtOH), was identified as **19**. The filtrate was column chromatographied on silica-gel, collecting 88 fractions of 30 ml. The following products were identified: nitrobenzene (CCl_4), **19** (CCl_4/CH_2Cl_2 1:3) and **16a** (CH_2Cl_2), m.p. 161–163° (from MeOH).

Reaction using methanol and trioctylmethylammonium chloride (*run* 42). A mixture of 2.65 g benzaldehyde, 3.08 g nitrobenzene, 0.163 g KCN, 1.2 g trioctylmethylammonium chloride and 0.8 g MeOH was kept at 80° for 48 hr. A white solid was formed, which was filtered, washed, dried and identified as KCl. Usual working up gave 28% methyl benzoate.

Reaction using isopropanol and trioctylmethylammonium chloride (*run* 43). A mixture of 2.65 g benzaldehyde, 3.08 g nitrobenzene, 0.163 g KCN, 1.0 g trioctylmethylammonium chloride and 1.5 g i-PrOH was kept at 80° for 96 hr. A solid was formed, which was filtered, washed with CH_2Cl_2 and dried to give 0.241 g of a white substance, m.p. 123–124° (from EtOH), identified as **19**. The filtrate was column chromatographed on silica-gel, recovering 0.625 g of **19** (CH_2Cl_2/$CHCl_3$ 3:1).

*Reaction using methanol and dibenzo-*18-*crown*-6-*ether* (*run* 46). A mixture of 2.65 g benzaldehyde, 1.54 g nitrobenzene, 0.673 g KCN, 0.265 g dibenzo-18-crown-6-ether, 0.8 g MeOH and 8 ml benzene was kept refluxing for 8 hr. A solid was formed, which was filtered off, washed with benzene and dried, to give 0.77 g of a white substance, m.p. over 250°, that was identified as **20**. The filtered soln was stored overnight in the refrigerator, affording 0.144 g of a pale yellow solid, m.p. 168–169° (from MeOH) identified as **28** (lit.[43] 170–172°). IR(KBr) ν_{max}: 3105–3085 (wide), 1600 cm^{-1}; NMR ($DCCl_3$) δ: 6,7–7,25 (m, 15H, ArH), 8,1 (ws, 1H, OH); MS *m/e*: 288 (M$^+$) (3%), 180 (100), 77 (75), 51 (32). The mother liquors were concentrated under reduced pressure and distilled, collecting two fractions: I, 2.435 g 80–100°/20 mmHg, and II, 0.704 g 100–120°/0,2 mmHg. Fraction I was a mixture of nitrobenzene, methyl benzoate and traces of benzaldehyde (NMR monitoring). Fraction II was column chromatographed on silica-gel and the following products were identified: **27**, 0.273 g (CCl_4), yellow solid, m.p. 70–71° (from hexane) (lit.[44] 71–72°). IR (CCl_4/0.1 mm) ν_{max}: 2240, 1610 cm^{-1}; NMR (CCl_4) δ: 7–8,2 (m, ArH); MS *m/e*: 206 (M$^+$) (100%), 205 (89,5) 180 (44), 77 (55); **16a**, 0.256 g (CCl_4/CH_2Cl_2 1:4), m.p. 161–163°. Using the same procedure as in run 46, but substituting alumina for silica-gel as the chromatographic adsorbent (CCl_4), **21**[45] was identified as product. IR (film)[46] ν_{max}: 2940, 2840, 1665, 1600 cm^{-1}; NMR (CCl_4) δ: 3,9 (s, 3H, CH_3), 6,55–7,2 (m, 10H, ArH); MS *m/e*: 211 (M^+) (81%), 210 (75), 180 (97), 105 (74), 77 (100) 51 (49).

Reaction using isopropanol and bibenzo-18-*crown*-6-*ether* (*run* 48). A mixture of 2.65 g benzaldehyde, 1.54 g nitrobenzene, 0.673 g KCN, 0.272 g dibenzo-18-crown-6-ether, 1.5 g i-PrOH and 8 ml benzene was refluxed for 14 hr. A solid was formed, which was filtered off, washed with benzene and dried to give 1.116 g of a white substance, m.p. over 250°, identified as **20**. The filtered soln was concentrated and distilled, collecting two fractions: I, 0.903 g at 80°/20 mmHg and II, 0.629 g at 120°/0.4 mmHg. Fraction I was a mixture of nitrobenzene, benzaldehyde and isopropyl benzoate (2.4%) (NMR monitoring). Column chromatography of fraction II on silica-gel gave 0.368 g of **27**, yellow solid, m.p. 70–71°, and 0.026 g of **16a**, m.p. 161–163°. The undistilled residue was treated with MeOH and 0.936 g of **19** were recovered. Total yields of different products are summarized in Tables 1, 2 and 3.

Reactions between benzoyl cyanide and alcohols—Synthesis of benzoyl cyanide

Procedure I[47]. 14 g cuprous cyanide, previously dried at 110°, were put into a 100 ml flask and 15 ml recently distilled benzoyl chloride were added. The mixture was shaked until all the solid was wet with benzoyl chloride, and then was heated at 225°, for 2 hr, with vigorous agitation every 15–20 min. The mixture was distilled at 350° (bath temp), collecting a pale yellow liquid which was redistilled under reduced pressure (22 mmHg). Two fractions were collected: I, 95–112° and II, 104–107°. Fraction II crystallized in bulk, giving a solid which was identified as benzoyl cyanide, m.p. 30–32° (lit.[48] 32–33°), IR (film)[48] ν_{max}: 1675 (C=O) (yield 42%).

Procedure II[49]. In a 500 ml 3-necked round-bottomed flask fitted with a thermometer, 45.12 g benzoyl chloride, 0.1 g tetrabutylammonium iodide and 300 ml CH_2Cl_2 were mixed (under N_2). After cooling at 0° 20 ml water and 15.78 g NaCN, were added with magnetic stirring. The reaction was monitored by IR spectroscopy (disappearance of the acid chloride band at 1745 cm^{-1} and appearance of the benzoyl cyanide band at 1675 cm^{-1}). The organic layer was decanted, dried and evaporated. The residue was distilled under reduced pressure, 31°/0.2 mmHg, recovering 16.8 g benzoyl cyanide (40%).

Reaction between benzoyl cyanide and methanol. 0.494 g benzoyl cyanide were mixed with 5 ml MeOH. The mixture was refluxed for 6 hr. Solvent was removed under reduced pressure. NMR spectrum of the residue stabilised the presence of methyl benzoate in 93% yield.

Reaction between benzoyl cyanide and benzoin. 0.521 g benzoyl cyanide were mixed with 0.85 g benzoin and 5 ml acetone (used as solvent) and the mixture was held at 65° for 7 hr. After filtering off the formed solid, the solvent was evaporated to give solid which recrystallized, from EtOH, to give a mixture of benzoin and benzoin benzoate (70% yield, based on NMR analysis).

Reaction between benzoyl cyanide and isopropanol. 0.285 g benzoyl cyanide were mixed with 10 ml isopropanol and the mixture was kept at 90° for 7 hr. Solvent was removed under reduced pressure. NMR spectrum of the residue showed isopropyl benzoate formation in a 83% yield.

Reaction between benzoyl cyanide and t-butanol (*high temp*). 0.25 g of benzoyl cyanide was mixed with 10 ml t-BuOH and the mixture was heated at 110° for 6 hr. Solvent was removed under reduced pressure, and 0.227 g of a white solid, m.p. 121–123°, identified as benzoic acid, were recovered (yield 98%),

Reaction between benzoyl cyanide and t-butanol (*low temp*). 0.25 g benzoyl cyanide was mixed with 10 ml t-BuOH and the mixture kept at room temp for 5 days. Solvent was removed under reduced pressure. Reactants were recovered unmodified.

Reaction between benzoyl cyanide, isopropanol and benzoin. 0.25 g benzoyl cyanide, 0.114 g isopropanol and 0.404 g benzoin were dissolved in a mixture of 10 ml acetone and 5 ml nitrobenzene. The mixture was kept at room temp for 7 hr. Solvent was evaporated under reduced pressure and a solid was formed, which was removed by suction filtration, washed with MeOH and dried, giving 0.3 g of benzoin benzoate, m.p. 123–124° (50%). NMR spectrum of the filtered solution showed only traces of isopropyl benzoate.

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