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Base-Induced Rearrangement of *O*-Benzoylbenzaldehyde Cyanohydrin to Benzil and the Further Reactions of Benzil

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O-Benzoylbenzaldehyde cyanohydrin has been found to form benzil in DMF in a base-catalysed reversible reaction. The possibility of using the reaction for the synthesis of unsymmetrical benzils from an aldehyde derivative and an acid derivative was investigated, but such a synthesis was made invalid by the further reaction of benzil with strong bases. The reaction of benzil with potassium *tert*-butoxide in DMF gave several products, among which the formation of two of them involved the anion of DMF and the formation of others included redox reactions.

In connection with an investigation on the electrochemical reduction in aprotic media of acylated derivatives of benzaldehyde cyanohydrin as a model compound for some synthetic pyrethroid insecticides, it became of interest to investigate the reaction of such compounds with base in *N,N*-dimethylformamide (DMF). *O*-Benzoylbenzaldehyde cyanohydrin (**1**) during cyclic voltammetry (CV) is reduced about −1.5 V vs. Ag/AgI showing a broad peak; on the return sweep an anodic peak is observed at −0.62 V vs. Ag/AgI and on the second cathodic sweep a corresponding cathodic peak is observed (Fig. 1). The two peaks are parts of a reversible system, and the potential of the system suggests that benzil (**2**) is formed. The results from cyclic voltammetry of **1** thus suggested that some kind of rearrangement of **1** took place during the experiment induced by the electrogenerated base, and we report here on the initial formation of **2** from **1** induced by base, together with a suggested reaction path. We have further investigated the further reactions of **2** with base in DMF.

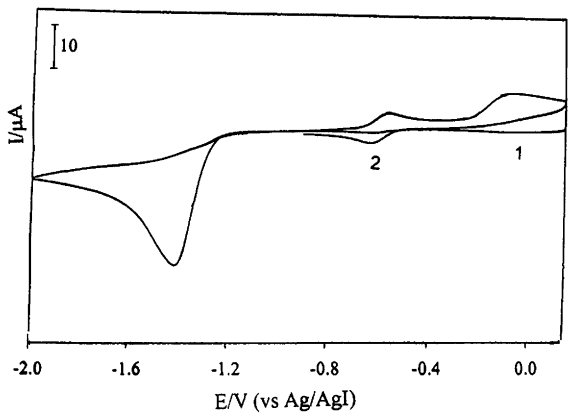

Fig. 1. Cyclic voltammetry of *O*-benzoylbenzaldehyde cyanohydrin (2 mM) in DMF–0.1 M $TBABF_4$ at a gold microelectrode, sweep rate 1 V s^{-1}: (1) first sweep; (2) second sweep.

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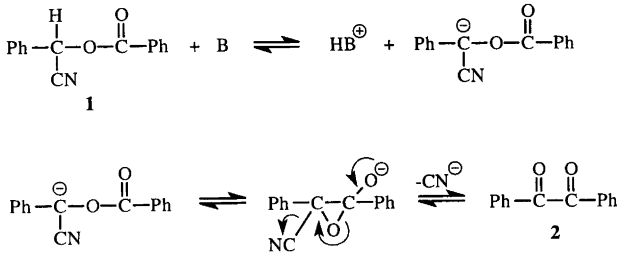
Results and discussion

During an electrochemical reduction it might be difficult to distinguish between steps caused by reduction and steps induced by electrogenerated base, so it was decided to separate the influence of electrogenerated base on **1** from the reduction of the compound. This could be done by using a probase which was reduced at a higher potential ('less negative') than that of **1**. The reduction of **1** begins at about −1.5 V vs. Ag/AgI in DMF; the classical probase azobenzene[1] is reduced at −0.88 V vs. Ag/AgI. CV of a mixture of **1** and azobenzene, reversed at −1.1 V, showed on the reverse sweep the oxidation of $\mathbf{2}^{-\cdot}$ and on the second sweep the reversible reduction of **2**.

It would be preferable for the probase to be reduced at a higher potential than **2**, but the radical anions of neither anthraquinone nor 4-nitrobenzonitrile were apparently basic enough to abstract a proton from **1** at a rate which produced **2** on the timescale of CV.

Oxygen (**3**) is reduced at a higher potential ('less negative') than both **2** and **1**, and the superoxide ion $\mathbf{3}^{-\cdot}$ is a strong base because the charge is localized; $\mathbf{3}^{-\cdot}$ is also a hydrogen atom abstractor.[2] CV of **1** in DMF

saturated with oxygen showed on the first sweep the reduction of **3** followed by the reversible reduction of **2** which means that $3^{-\cdot}$ is able to induce the rearrangement. As CV of **1** to which *tert*-butoxide has been added showed formation of **2** it seems likely that the superoxide ion in this case acted faster as a base than as a hydrogen atom acceptor; the reason is probably that the anion of **1** reacts fast in an irreversible reaction whereas in many other cases the loss of a proton is a reversible process. On the basis of this the following scheme has been suggested.



Scheme 1.

In Scheme 1 the methine proton is abstracted by the base; the methine proton is made acidic by the substituents, the cyano, benzoyloxy and phenyl groups. The carbanion is suggested to add to the carbonyl group in an intramolecular nucleophilic addition with formation of an epoxide intermediate. The carbonyl group is re-established with simultaneous opening of the epoxide by cleavage of the carbon–oxygen bond and loss of the cyano group with formation of benzil.

The proposed reaction route is similar to a part of a scheme suggested[3] for the cathodic reduction of benzoyl cyanides in acetonitrile (MeCN), when the backward reactions are occurring (from **1** to **2**). **1** was found among the products from the cathodic reduction of benzoyl cyanide in anhydrous MeCN, whereas benzil was the main product in a MeCN–H_2O (70–10 ml) mixture. The similarities between the products from the electrochemical reduction of benzoyl cyanide in acetonitrile and the base-catalysed rearrangement of *O*-benzoylbenzaldehyde cyanohydrin in DMF suggest that the reactions **1** ⇄ **2** are reversible.

The initial investigations of the reaction were complicated by the fact that a solution of **1** in DMF in the GLC analysis gave a mixture of **1** and **2**. Heating of **1** in DMF gave a mixture of **1** and **2** in a proportion of about 2:1. Prolonged heating did not change the composition of the mixture, supporting the contention that an equilibrium existed between **1** and **2** catalysed by base. GLC of **1** in dichloromethane gave a single signal from **1** thus indicating that DMF was basic enough or contained a base strong enough to induce the equilibrium at elevated temperatures.

If the proposed reaction route were correct it should be expected that *O*-benzoylbenzaldehyde cyanohydrins substituted differently in the benzene rings would form unsymmetrical benzils. Treatment of *O*-benzoyl-4-methoxybenzaldehyde cyanohydrin with electrogenerated base showed in CV a reversible redox system at the same potential as that of authentic 4-methoxybenzil in accordance with Scheme 1.

The base-induced rearrangement of derivatives of **1**, which are prepared by acylation of a benzaldehyde cyanohydrin, could, in principle, be an attractive way of synthesizing unsymmetrical benzils from an aldehyde derivative and an acid derivative. However, it is well known that benzil rearranges to benzilic acid on reaction with hydroxide ions and to *tert*-butyl benzilate on treatment by potassium *tert*-butoxide in refluxing benzene.[4] Reaction of electrogenerated superoxide ion with benzil under preparative conditions yields benzoic acid.[5]

It was found that treatment of **1** with potassium *tert*-butoxide gave a reaction mixture similar to that obtained from treatment of **2** with the same base. It was thus of interest to investigate the reactions of benzil with *tert*-butoxide in DMF, as any attack of the base might destroy the benzil formed in the rearrangement and thus invalidate the synthesis of mixed benzils from analogues of **1**. Treatment of **2** in DMF with sublimed potassium *tert*-butoxide destroyed the benzil and resulted in a mixture of compounds (**4**, **5**, **6**, **7** and **8**) described below; a discussion of how these compounds might be formed is also presented. The yields are isolated yields of products after column chromatography which partly explains the relatively poor material balance (about 60%).

Benzoin (15%) **4**; it has often been observed that in a reaction with strong base some reduction takes place. An example is the finding by Paradisi and Scorrano[6] that the reaction of 4-chloronitrobenzene with potassium 2-propoxide in 2-propanol at 75 °C under argon gave 57% 4,4′-dichloroazoxybenzene, 12% 4-chloroaniline, 6% of the formylated aniline and 5.6% of the dichloroazobenzene. The point most difficult to explain in the above reaction is the initial step; the observation of chloronitrobenzene radical anion at the beginning of the reaction suggests that the reduction is not a simple hydride transfer reaction. An outer-sphere electron transfer (ET) is too endergonic to be viable.

The reduction of benzil to benzoin may involve an inner-sphere ET from some base followed by abstraction of a hydrogen atom from DMF, as DMF is a reasonably good hydrogen-atom donor;[7] a base-induced hydride-ion transfer from benzhydrol, suggested to be the precurser of benzophenone, is another possibility.

Benzophenone (**5**) is isolated in a few percent yield; probably more is formed during the reaction as the compound seems to be an intermediate during the formation of **6** and **7**. Benzophenone might be formed through a benzilic acid type rearrangement catalysed by *tert*-butoxide or another base followed by decarboxylation to benzhydrol. As benzil is much more easily reduced than benzophenone a base-catalysed reduction by hydride transfer from benzhydrol to benzil yielding benzoin and benzophenone should be possible. An alternative possibility might be cleavage of *tert*-butyl benzil-

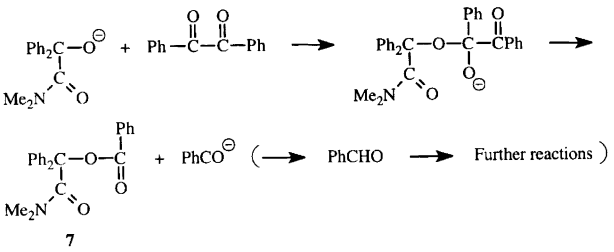
ate, formed in the benzilic acid rearrangement with *tert*-butoxide as base, directly to benzophenone and *tert*-butyl formate. The pK_a of *tert*-butyl formate would not be expected to be very different from the pK_a of DMF.

A product suggested to be *N,N*-dimethyl-2,2-diphenyl-2-hydroxyacetamide (**6**) was isolated in various yields (15–23%). The structure of **6** was suggested mainly from the ^{1}H NMR spectrum. Singlets at δ 2.55 and 3.12, broadened as generally found in amides due to the relatively slow rotation around the carbon–nitrogen bond, indicated a dimethylaminocarbonyl group, a singlet (1 H, broad) a hydroxy group and 10 aromatic hydrogens on two benzene rings. A prominent peak in MS at *m/z* 183 is due to a fragment after loss of a dimethylaminocarbonyl group from **6**; no molecular peak was observed and the MS is thus similar to the MS observed for benzilic acid, where no molecular peak is found due to loss of carbon dioxide.

Compound **6** could be formed by an attack of the anion of DMF on benzophenone. Different values of the autoprotolysis constant of DMF have been reported (23–31),[8] and the pK_a of 2-methyl-2-propanol in DMSO has been indicated to 32.[8] The conditions in DMF are probably not very different from those in DMSO, so at least some anion of DMF should be formed on addition of potassium *tert*-butoxide to DMF, Scheme 2. The involvement, at some stage, of the radical $Me_2NCO^{\cdot}$, obtained by hydrogen abstraction from DMF, might be a possibility, but it seems less likely.

A compound suggested to be *N,N*-dimethyl-2,2-diphenyl-2-benzoyloxyacetamide (**7**) has been isolated in various yields (11–18%), the more **7** the less **6**. The structure of **7** was established from the following facts. The IR spectrum showed two carbonyl groups at 1723 (ester) and 1657 cm^{-1} (amide) in accordance with the signals at δ 168.9 and 164.5 in the ^{13}C NMR spectrum. Broad signals (^{1}H NMR) at δ 2.73 and 3.05, similar to those found in **6**, showed a dimethylaminocarbonyl group. ^{1}H NMR spectroscopy further suggested three benzene rings, one being a benzoyl group and two being equal; this was substantiated by signals from eight different carbon signals between 127 and 140 ppm in the ^{13}C NMR spectrum. A small molecular peak at *m/z* 359 was in accordance with the suggested structure of **7**.

The acylation of **6** to **7** might involve an attack of the anion of **6** on benzil. This would require the expulsion of a benzoyl anion which would be protonated on carbon to give benzaldehyde. Under the prevailing strongly basic conditions a Cannizzaro reaction would probably induce the formation of benzoate and benzyl alcohol, Scheme 3.



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Scheme 3.

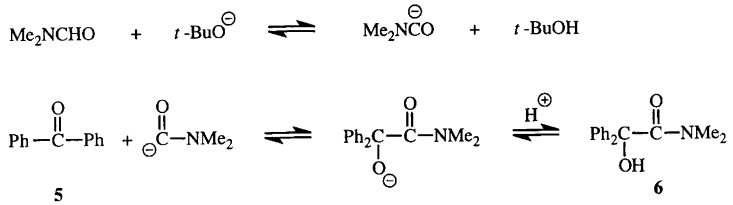
Benzoylbenzoin (**8**) (yield 5%) could be formed by an attack of benzoin anion on benzil, analogous to the reaction between **6**$^-$ and benzil leading to **7** suggested above.

Benzoic acid, isolated in 10% yield, may be formed in different ways (e.g. Cannizzaro reaction, oxidation of the benzoyl anion) and its formation is not discussed here.

Conclusions

The investigation shows that different kinds of base in DMF can induce a rearrangement of derivatives of *O*-benzoylbenzaldehyde cyanohydrin (**1**) to a derivative of benzil (**2**). Even DMF (or small amounts of basic impurities still found in DMF purified through a column of alumina) is basic enough to catalyse the rearrangement of **1** to **2** at elevated temperatures; it is noticeable that the heating occurring during the injection of a sample of **1** dissolved in DMF for GLC analysis is enough to cause some rearrangement, so that peaks due to both **1** and **2** are obtained. However, the base necessary to induce the rearrangement of **1** to benzil also reacts with **2**, so the basic rearrangement of **1** is not a viable synthesis of derivatives of benzil.

The reaction of benzil with a strong base, such as potassium *tert*-butoxide, in DMF gave a mixture of compounds; such reactions invalidated the synthesis of unsymmetrical benzils from an aldehyde derivative and an acid derivative. The reaction mixture consisted of some expected compounds (benzilic acid derivatives) and two new compounds (**6** and **7**) which were apparently formed through attack of the anion of DMF on **2**. In the literature a range of values[8] for the autoprotolysis constant of DMF can be found; it would be desirable to



Scheme 2.

have a reliable value of the pK_a value of DMF in view of the extensive use of DMF as a solvent for electrochemical measurements.

Experimental

Materials. *O*-Benzoylbenzaldehyde cyanohydrin (**1**), as well as its derivatives, were synthesized from benzaldehyde, sodium cyanide and benzoyl chloride according to the literature.[9] Potassium *tert*-butoxide was sublimed at 220 °C *in vacuo*. The supporting electrolyte, Bu_4NBF_4, and the solvent, *N,N*-dimethylformamide (DMF), were purified by standard procedures. The electrolyte solution was dried through a column of activated alumina just before each experiment.

Equipment. ^1H NMR and ^{13}C NMR spectra were measured on a 200 MHz spectrometer in $CDCl_3$. GC was performed on a Hewlett–Packard 5890 A gas chromatograph. Cyclic voltammetry was recorded at a gold electrode for samples in DMF–0.1 M Bu_4NBF_4. The potential of the reference electrode Ag/AgI in DMF is −0.40 V vs. SCE.

*Heating of **1** in DMF.* A solution of **1** (50 mg) in 2 ml dried DMF was heated under reflux. TLC and GC were used to monitor the reaction. Usually some benzil was formed after several minutes. The yield of benzil increased with the reflux, but after several hours it reached a maximum value (not more than 30%).

Reaction of benzil with Bu^{t}OK. Equimolar amounts of **1** (1 g) and potassium *tert*-butoxide (0.534 g) were added to 20 ml dried DMF and stirred under nitrogen at room temperature. After 1 h, the solution was quenched with water and acidified with hydrochloric acid. The solution was extracted three times with diethyl ether and the ether phase was washed with water three times. After being dried ($MgSO_4$), the solution was evaporated. The mixture was separated by column chromatography on silica with ethyl acetate–petroleum ether 4:1 as the eluent. Isolated were benzoin (**4**) (15%), benzoic acid (10%), benzophenone (**5**) (3%), *N,N*-dimethyl-2,2-diphenyl-2-hydroxyacetamide (**6**) (15–23%), *N,N*-dimethyl-2,2-diphenyl-2-benzoyloxyacetamide (**7**) (11–18%), benzoylbenzoin (**8**) (5%) together with traces of benzil.

N,N-Dimethyl-2,2-diphenyl-2-hydroxyacetamide (**6**) 15–23% yield. ^1H NMR ($CDCl_3$): δ 2.55 (s, 3 H), 3.12 (s, 3 H), 6.0 (s, 1 H), 7.3–7.4 (m, 10 H). MS (*m/z*, %): 183 (42), 165 (22), 105 (100), 77 (55), 72 (23).

N,N-Dimethyl-2,2-diphenyl-2-benzoyloxyacetamide (**7**) 11–18% yield. M.p. 158–160 °C. ^1H NMR ($CDCl_3$): δ 2.73 (s, 3 H), 3.05 (s, 3 H), 7.2–7.4 (m, 6 H), 7.48–7.6 (m, 6 H), 7.65 (t, 1 H), 8.22 (d, 2 H). ^{13}C NMR ($CDCl_3$): δ 37.978, 38.282, 87.598, 127.260, 128.135, 128.616, 129.235, 130.005, 130.454, 134.130, 140.879, 164.554, 168.905. MS (*m/z*, %): 359 (1, M^+), 287 (33), 254(6), 238 (20), 210 (28), 165 (47), 105 (100), 77 (74), 72 (49), 51 (13). IR (KBr): 1723, 1657.

Benzoylbenzoin **8**: m.p. 124–126 °C (lit.[10] 125 °C), yield 5%, ^1H NMR ($CDCl_3$): δ 7.1 (s, 1 H), 7.3–7.6 (m, 11 H), 8.07 (d, 2 H), 8.13 (d, 2 H). ^{13}C NMR ($CDCl_3$): δ 78.445, 128.920, 129.193, 129.363, 129.654, 129.836, 130.503, 133.883, 134.021, 134.251, 135.196, 166.541, 194.197. MS (*m/z*, %): 316 (0.3, M^+), 211 (66), 165 (6), 105 (100), 77 (62).

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