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The Benzil Rearrangement Reaction: Trapping of a Hitherto Minor Product and Its Application to the Development of a Selective Cyanide Anion Indicator

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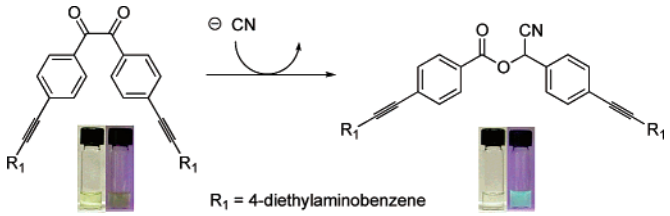
ABSTRACT



The isolation and characterization of an intermediate from the benzil–cyanide reaction is reported. The use of this trapping chemistry to produce a chemical indicator for the cyanide anion is described. It relies on the synthesis and reaction of a π-extended analogue of benzil. Addition of tetrabutylammonium cyanide to organic solutions of this species, referred to as compound 3 in the text, gives rise to a dramatic change in both color and fluorescence properties.

Cyanide-mediated reactions have a time-honored place in organic chemistry and include such classic transformations as the Stetter, Franchimond, and Strecker syntheses, as well as the benzoin condensation. In addition, cyanide salts are widely used in gold mining, electroplating, and metallurgy.[1] However, even small amounts of the cyanide anion are extremely toxic to living creatures as the result of binding to cytochrome *c* and inhibition of the mitochondrial electron-transport chain.[2] Therefore, any accidental release of cyanide salts can result in serious environmental damage. There is thus a cogent need for cyanide-selective receptors and sensors. Many of the cyanide anion receptors reported to date have relied on hydrogen bonding motifs[3] and, as a consequence, have generally displayed poor selectivities relative to other anions.[4] To overcome this limitation, receptors based on oxazines[5] and acridinium salts[6] have been developed that take advantage of nucleophilic reactions involving cyanide. However, the reactions in question require specific conditions, such as the use of elevated temperatures or basic media. Another interesting cyanide anion receptor, dipyrrole carboxamide,[7] also takes advantage of a putative

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(4) The basicity of the anions in question (including cyanide) could be contributing to the observed sensing and competition effects. See: (a) Anzenbacher, P., Jr.; Tyson, D. S.; Jursíková, K.; Castellano, F. N. *J. Am. Chem. Soc.* **2002**, *124*, 6232−6233. (b) Chung, Y. M.; Raman, B.; Kim, D.-S.; Ahn, K. H. *Chem. Commun.* **2006**, 186−188.

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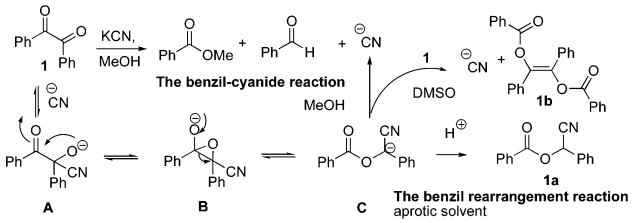
nucleophilic reaction.[8] However, in no cases were the proposed addition products isolated, making it difficult to verify the suggested mechanism of action. Given this uncertainty, we felt it would be advantageous to develop a cyanide-driven reaction that (*i*) operates at room temperature, (*ii*) has a clear mechanistic signature, and (*iii*) could be exploited for the development of off-the-shelf indicators[9] for this toxic agent. We now report such a reaction. It involves the optimized trapping of a single product from a hitherto little-explored, cyanide-induced transformation called the benzil rearrangement.

The benzil rearrangement, and the mechanistically related benzil−cyanide reaction (Scheme 1), is believed to proceed

Scheme 1. Proposed Mechanisms of the Benzil−Cyanide Reaction and the Benzil Rearrangement Reaction



through intermediate **C**.[10] While this intermediate represents a species whose existence is widely accepted, to the best of our knowledge, the corresponding protonated mandelonitrile benzoate product **1a** has yet to be isolated as a major product from benzil.[11] As detailed below, this species may be obtained in good yield via the appropriate choice of conditions. Moreover, the use of benzil analogues permits the dosimeter-type detection of the cyanide anion in organic media.

Intermediate **C** has long been considered to be unstable under typical benzil−cyanide-type reaction conditions. In fact, in alcoholic solvents, intermediate **C** undergoes scission to produce benzaldehyde and the alcohol-derived benzoate ester, whereas in DMSO, the stilbenediol benzoate diester **1b** is formed.[12] However, we have now found that the use of aprotic solvents (i.e., acetonitrile, $CHCl_3$, and EtOAc), as well as a more organic soluble cyanide source (tetrabutylammonium cyanide, TBA·CN), allows the protonated form of intermediate **C** (compound **1a**) to be isolated in decent

Table 1. Products from the Benzil Rearrangement[a]

entry	substrate	product	yield[b]
1	R_1 = H	R_1 = H, **1a**	83
2	R_1 = 3-Methoxyphenyl	R_1 = 3-Methoxyphenyl, **2a**	80
3	R_1 = 4-diethylaminobenzene	R_1 = 4-diethylaminobenzene, **3a**	67

[a] All reactions were run in chloroform on a 20 mg scale (diketone substrate). Tetrabutylammonium cyanide (1.2−2 equiv) was added to a solution of substrate (6 mL, $CHCl_3$) at 25 °C. The reaction was deemed complete after 20 min (cf. Supporting Information). [b] Isolated yields.

yield from benzil analogues; cf. Table 1. Our results thus provide direct support for intermediate **C** in benzil−cyanide-type reactions.

An interesting feature of the rearrangement of **1** to **1a** is that it serves to sever the conjugation pathway between the two aryl carbonyl groups originally present in benzil. We thus imagined that this rearrangement could be used to produce a specific, cyanide-mediated color change, provided a suitably colored benzil derivative could be obtained. To test this hypothesis, the π-extended system **3** was prepared; it was synthesized in 70% yield via the Sonogashira coupling of dibromobenzil with *N*,*N*-diethyl-4-ethynylbenzenamine (cf. Supporting Information).[13]

The benzil rearrangement reaction of **3** was monitored by UV−vis spectroscopy, as shown in Figure 1. In the absence of an added anion, the absorption maximum of **3** (dissolved in ethyl acetate appears at 412 nm). After the addition of 3 equiv of tetrabutylammonium cyanide, a large bathochromic shift was observed ($\Delta\lambda_{max}$ = 56 nm), with all spectral changes being complete within 1 min (Figure 1a). This blue shift is reflected in a change in the color of the solution from yellow to colorless (Figure 1b), allowing for facile qualitative analysis.[14] The fact that **3a** is fluorescent also allowed the cyanide-mediated conversion to be followed using a laboratory UV lamp (Figure 1c), with the limit of detection [LoD] being ca. 20 μM in organic solution.

To evaluate the selectivity of receptor **3**, 3 equiv of various potentially competing anions (studied as the corresponding tetrabutylammonium salts), including OH^-, F^- (as the trihydrate), N_3^-, AcO^-, Cl^-, HSO_4^-, and $H_2PO_4^-$, were each

(7) Chen, C.-L.; Chen, Y.-H.; Chen, C.-Y.; Sun, S.-S. *Org. Lett.* **2006**, *8*, 5053−5056.

(8) An interesting reaction-based approach to developing fluorescent (but non-colorimetric) cyanide anion receptors, involving the use of ammonium boranes, was reported during the time this work was being written up for publication. See: Hudnall, T. W.; Gabbai, F. P. *J. Am. Chem. Soc.* **2007**, *129*, 11978−11986.

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(11) Previous workers isolated **1a** in 18% yield while recovering benzil in 60% yield: Clerici, A.; Porta, O. *J. Org. Chem.* **1994**, *59*, 1591−1592.

(12) Trisler, J. C.; Frye, J. L. *J. Org. Chem.* **1965**, *30*, 306−307.

(13) *N*,*N*-Dimethyl-4-ethynylbenzenamine is commercially available. *N*,*N*-Diethyl-4-ethynylbenzenamine was synthesized according to a literature procedure: Miki, Y.; Momotake, A.; Arai, T. *Org. Biomol. Chem.* **2003**, *1*, 2655−2660.

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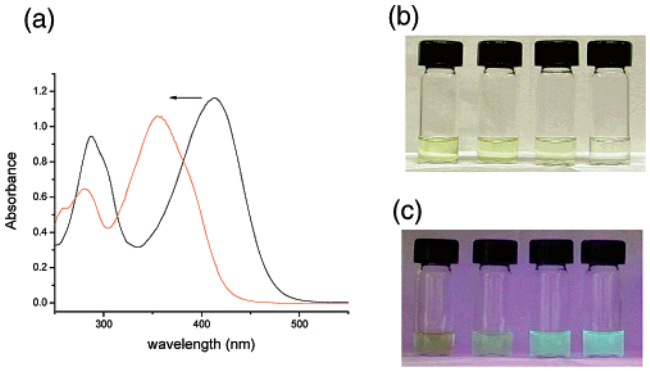

Figure 1. (a) UV−vis spectra of receptor **3** (2.13×10^{-5} M in ethyl acetate) recorded before and 1 min after the addition of tetrabutylammonium cyanide (TBA·CN, 3 equiv in acetonitrile). (b) Color changes observed upon the addition of varying quantities of TBA·CN (as a 4.65×10^{-3} M stock solution in acetonitrile) to solutions of receptor **3** (2.13×10^{-5} M in ethyl acetate). From left to right: 0, 1, 2, and 3 equiv. (c) Fluorescence changes observed at 365 nm with a laboratory UV lamp upon the addition of varying quantities of TBA·CN (as a 4.65×10^{-3} M stock solution in acetonitrile) to solutions of receptor **3** (2.13×10^{-5} M in ethyl acetate). From left to right: 0, 1, 2, and 3 equiv.

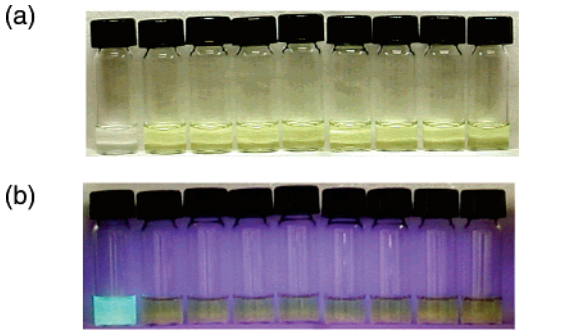

Figure 2. (a) Color changes observed upon the addition of various anions (3 equiv in ethyl acetate) to solutions of receptor **3** (2.13×10^{-5} M in ethyl acetate). From left to right: CN^-, OH^-, F^-, N_3^-, AcO^-, Cl^-, HSO_4^-, $H_2PO_4^-$, and no added anion. (b) Fluorescence change observed upon excitation at 365 nm with a laboratory UV lamp after the addition of various anions (3 equiv in ethyl acetate) to solutions of receptor **3** (2.13×10^{-5} M in ethyl acetate). From left to right: CN^-, OH^-, F^-, N_3^-, AcO^-, Cl^-, HSO_4^-, $H_2PO_4^-$, and no added anion. All anions were used in the form of their respective tetrabutylammonium (TBA) salts. Some of insoluble anions (viz. CN^-, OH^-, HSO_4^-, and $H_2PO_4^-$) were dissolved in acetonitrile prior to the addition.

added to organic solutions of **3**. In no case was a change in color observed. This stands in marked contrast to what was seen when 3 equiv of CN^- was added (cf. Figure 2). Compound **3** thus appears to be exceptionally selective for cyanide. In particular, it shows great selectivity over basic anions, something that is usually not seen in the case of hydrogen-bonding-based receptors and sensors.

Using system **3**, the presence of cyanide can be easily detected in organic media, either by eye or via the use of a laboratory UV lamp. Effective as it is, however, it must be stressed that compound **3** is not a classic chemosensor. Rather, since an irreversible chemical reaction is used to produce the colorimetric response, it acts as cyanide-specific anion indicator and is subject to all the caveats that this term implies (i.e., intensity of response being potentially dependent on both [CN^-] and [**3**], possible kinetic limitations, etc.). However, its convenience and the possibility for further modifications to the central benzil core led us to predict that **3** and its analogues could have a role to play in the detection of cyanide anion in organic media or under interfacial (e.g., mixed phase or polymer supported) conditions. In addition, because a well-defined covalent adduct is formed, the present approach could provide materials that allow for cyanide remediation as well as detection. Explorations of these possibilities are currently underway, as is a search for other reactions that might allow for anion recognition.[15]

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Supporting Information Available: Synthetic experimental and characterization data for compounds **2**, **2a**, **3**, and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) There is increasing interest in the development of reaction-based sensors and indicators within the generalized molecular recognition field. For recent work, see, for instance: (a) Albers, A. E.; Okreglak, V. S.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 9640−9641. (b) Song, F.; Garner, A. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 12354−12355.