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An unexpected formation of benzoyl benzoin from benzil during the attempted Knoevenagel type condensation with dimethylmalonate (or malononitrile)

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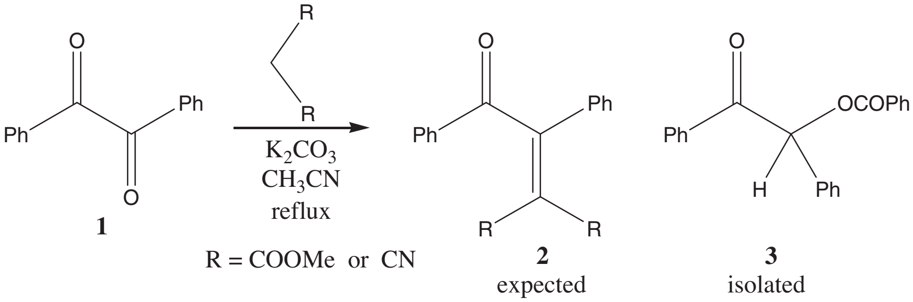
ABSTRACT

An unexpected product, 2-oxo-1,2-diphenylethyl benzoate (benzoyl benzoin), was isolated during the attempted Knoevenagel reaction of benzil and dimethylmalonate (or malononitrile) in the presence of potassium carbonate. The product was confirmed by spectral analysis as well as by single crystal studies and a mechanism is proposed to explain its formation.

The classical Knoevenagel reaction of aldehydes and ketones with molecules containing active methylene group, like Z-CH_2-Z where Z is electron withdrawing group, gives conjugated systems.[1] As a part of our ongoing research project we were keen to carry out Knoevenagel condensation on 1,2-diketo compounds like benzil **1** to prepare mono substituted conjugated system **2**. Benzil is known to react with various nucleophilic species like hydroxide to undergo benzilic acid rearrangement,[2] diphenyl acetone to give tetraphenyl cyclopentadienone,[3] 1° amines to form mono imines,[4] etc. Benzils are also known to form other heterocyclic compounds when treated with nucleophilic reagents under specific conditions.[5] A bis-imine prepared from benzil with 2 equiv of chiral 1° amines is used as a ligand for Mo-catalyzed reactions[6] and another one prepared from aminophenols is used in catalytic oxidation reactions.[7]

However, a number of attempts in our laboratory to carry out this conversion could not furnish the desired compound **2**. Initially, the reaction of benzil and dimethylmalonate was conducted in dry acetonitrile in the presence of potassium carbonate to facilitate the anion formation. Two new products were detected in the reaction mixture, but on separation none of them was the expected compound **2**. One of the lesser polar products was isolated and identified to be 2-oxo-1,2-diphenylethyl benzoate (benzoyl benzoin), **3** by spectroscopic analysis and also by comparison of



Scheme 1. Attempted Knoevenagel reaction of benzil.

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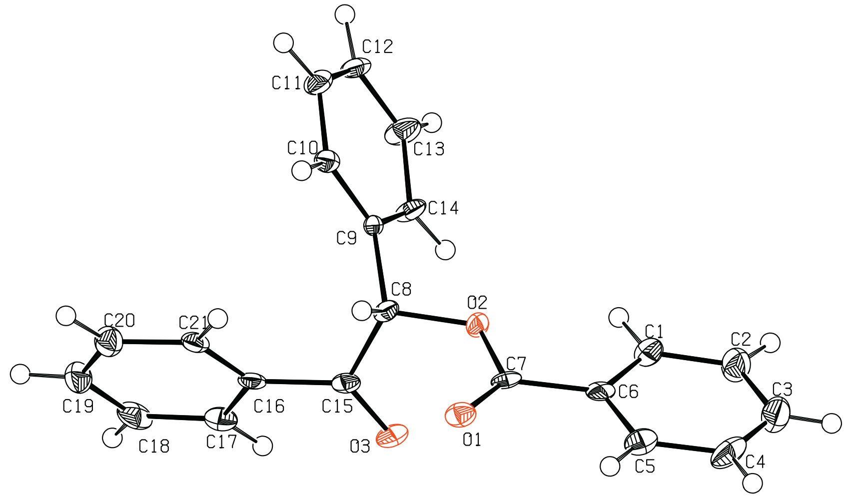
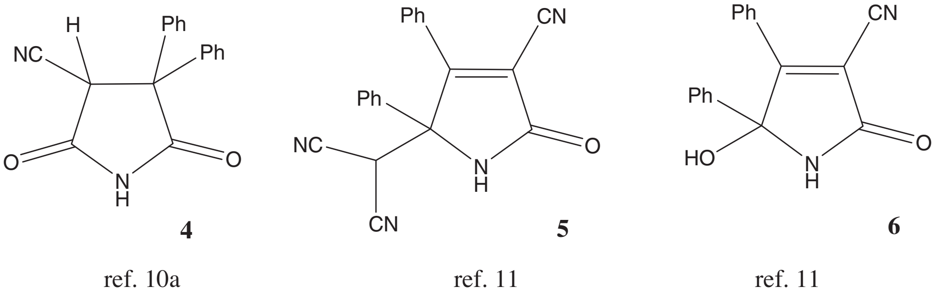
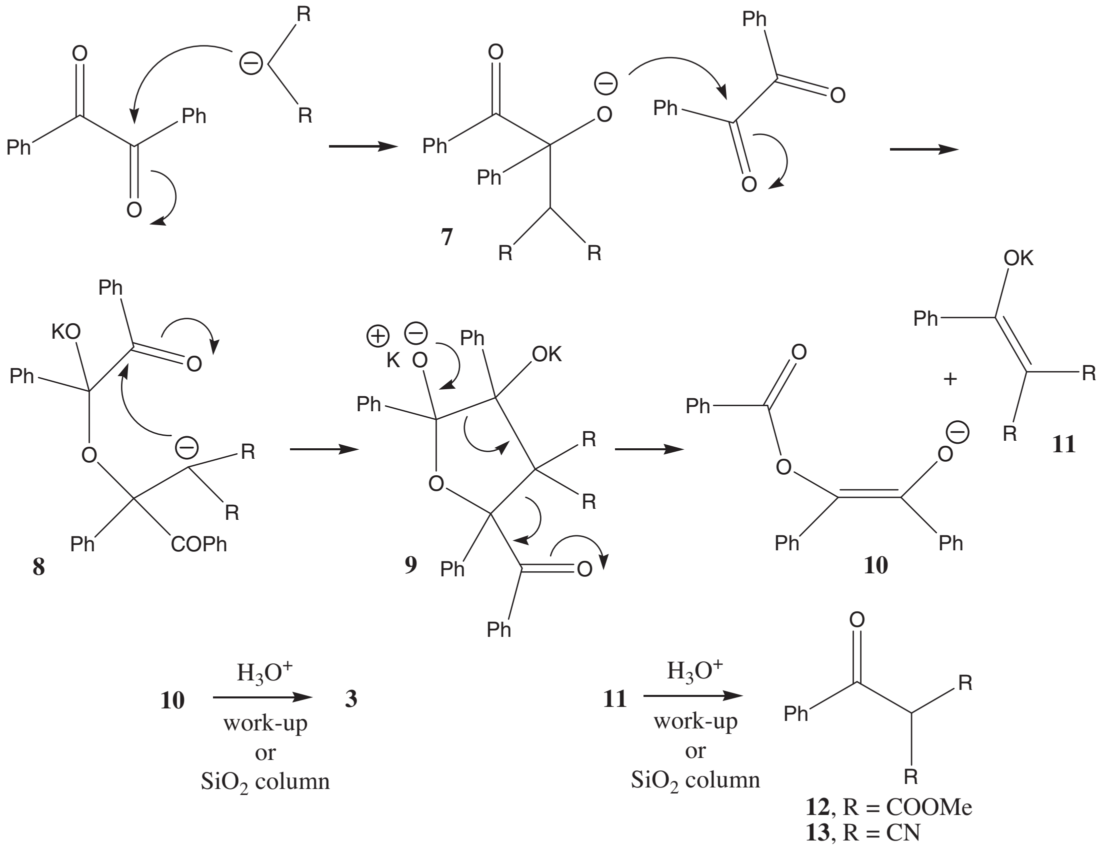


Figure 1. ORTEP diagram of the organic compound **3** with atom numbering scheme (50% probability factor for the thermal ellipsoids.[9]



Scheme 2. Observed products from earlier literature.



Scheme 3. Suggested mechanism to explain formation of **3** from benzil **1**.

melting point with that of the reported one[8] (see Scheme 1). Interestingly, the same product **3** was formed when reaction of benzil was carried out with malononitrile. It was noteworthy to observe the complete absence of this product when neither dimethylmalonate nor malononitrile was used and **1** was heated only with K_2CO_3 in acetonitrile.

The structure of **3** was also established by single crystal X-ray analysis as shown in Figure 1.[9]

Reaction of benzil with malononitrile is first reported by Junek et al.[10] to observe the formation of 2-benzoyl-2-phenyl-ethylene-1,1-dicarbonitrile (**2**; R═CN) and 2,5-dioxo-4,4-diphenyl-pyrrolidine-3-carbonitrile **4**. This reaction was reinvestigated by Ducker and Gunter[11] and have proposed the formation of two other heterocyclic products, 4′-cyano-5′-oxo-2′,3′-diphenyl-3′-pyrrolin-2′-ylmalononitrile 5 and 5-hydroxy-2-oxo-4,5-diphenyl-3-pyrrolin-3-carbonitrile **6 (see** Scheme 2).

The same product **3** is reported to have formed when benzil is treated with cyanide ion in the presence of benzaldehyde and the key step in the mechanism involves 1,2 C–O shift.[8a] Such a possibility can be ruled out in the present case as the reaction does not have cyanide ion or benzaldehyde. Another reaction of benzil with cyanide ion is reported to be following a different mechanistic pathway.[12]

The proposed mechanism of the formation of product **3** from benzil is outlined in Scheme 3. The fact that the reaction does not proceed in the absence of either a base or dimethylmalonate or malononitrile clearly indicate that the reaction starts by a nucleophilic attack of the anion of active methylene to one of the carbonyls of benzil. The intermediate **7** may further attach to another benzil molecule to form intermediate **8**, which can undergo an intramolecular nucleophilic attack on the second carbonyl of the second benzil molecule to give a tetrahydrofuran intermediate **9**. Intramolecular ring opening of this highly substituted intermediate **9** is quite possible to give stabilized species **10** and **11**, which during work up can give **3** and **12**/**13** as products, respectively. Product **12** was isolated (43% yield) and its structure was confirmed by spectral analysis (mass and ^{1}H NMR) when dimethylmalonate was used with benzil.

Our attempts to carry out identical reaction with camphorquinone and phenanthraquinone with dimethylmalonate did not result in similar reaction and products from usual Knovenagel condensation were detected.

In this short communication we have thus presented the unusual observation when benzil was treated with dimethylmalonate or malononitrile in the presence of a base.[13]

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13. *General reaction condition:* Benzil (0.25 g, 1.19 mmol) was dissolved in acetonitrile (10 mL) in a two neck r.b. flask attached with water condenser. To this mixture K_2CO_3 (0.411 g, 2.98 mmol) was added and stirred for few minutes at room temperature and dimethylmalonate (0.157 g, 1.19 mmol) was added drop wise. The reaction mixture was stirred at reflux temperature for 72 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuum, the residue was taken in saturated aqueous NH_4Cl, extracted with ethyl acetate (3×25 mL). The organic layer was washed with dilute aqueous NaOH (2×25 mL) and the ethyl acetate layer was dried on anhydrous sodium sulfate, evaporated in vacuum. The crude white solid was purified over silica gel column (petroleum ether/ethyl acetate 95:5) to obtain pure compound **3** (0.175 g, 47% Y) and further purified by recrystallization from acetonitrile. The aqueous NaOH layer was combined and acidified with cold dilute HCl, and extracted with ethyl acetate (3×25 mL), dried over anhydrous sodium sulfate, concentrated in vacuum to obtain a pale yellow liquid as crude product, purified over silica gel column (petroleum ether/ethyl acetate 90:10) to obtain pure compound **12**, as colorless liquid (0.12 g, 43% Y). 2-Oxo-1,2-diphenylethyl benzoate (benzoyl benzoin), **3**: Mp = 130–132 °C. IR: ν cm^{-1}(KBr): 3070 (C–H stretch aromatic), 2952 (C–H stretch aliphatic), 1714 (Ar–COO), 1695 (Ar–CO), 1597, 1451, 1353, 1314, 1281, 1247, 1174, 1118, 1068, 1029, 956, 853, 758, 702, 590. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.14 (2H, m), 8.05–8.02 (2H, m), 7.62–7.54 (4H, m), 7.49–7.39 (7H, m), 7.12 (1H, s). ^{13}C NMR (100 MHz $CDCl_3$): δ 193.7, 166.1, 134.66, 133.7, 133.6, 133.4, 130.0, 129.4, 129.2, 128.9, 128.7, 128.5, 77.9. Mass (EI$^+$): *m*/*z* (%) 316.07, 211.02 (17%), 106.01 (9%), 104.96 (100%), 77.01 (36%). 2-Benzoyl dimethylmalonate, **12**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.89 (2H, m), 7.65–7.60 (1H, m), 7.52–7.46 (2H, m), 5.36 (1H, s), 3.81 (6H, s). Mass (EI$^+$): *m*/*z* (%) 237.2 (M+1), 236.3 (46%), 235.4 (100%), 205.1 (24%), 175.8 (23%), 106.1 (49%), 105.3 (72%), 104.3 (87%), 77.3 (49%), 76.5 (66%), 78.1 (11%), 58.9 (13%).