# Summer Scholar Report
Toward New Organic Solid State Reactions

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Introduction

The objective of this research is the discovery and development of new lattice-controlled organic solid-state reactions. Reasons for interest in such reactions include that the rigid structure of the solid state allows for considerable regiospecificity and stereoselectivity, as well as the possibility to synthesize systems that are otherwise difficult to access. Moreover, such reactions are "environmentally friendly" as they do not utilize a solvent. These reactions can be initiated either thermally or by ultraviolet light.

The [2+2] pi dimerization of cinnamic acids[1,2] **1** (X= - OH) and amides, usually accomplished with ultraviolet (uv) light or sunlight, is the best known of molecular solid-state reactions. Since the detailed role of the chromophore in the cinnamic reaction is not clear, a modification of the chromophore by substitution with nitrogen is of interest, and the initial subjects for investigation are shown in Figure 1. The molecular structure of cinnamic acid is regarded as consist- ing of an aromatic ring, a multiple bond, and a hydrogen-bonding group. In the current research, the aromatic groups could include benzene, naphthalene, pyridine, quinoline, thiophene, furan, and pyrrole. The multiple bonds could include carbon-carbon double and triple bonds and carbon-nitrogen double bonds. The hydrogen-bonding groups would be carboxyl, amide, and urea.
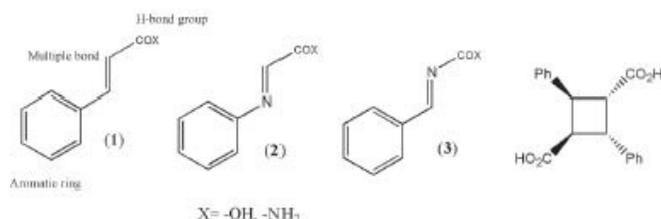
Figure 1: *Cinnamic acid, amide, and related structures; structure of the photodimer of the α-form of 1*

Imesatin

A synthesis of **2** (X=-OH) was attempted by reaction of aniline with glyoxylic acid monohydrate[3]. From its IR spectrum, the major product was a determined to be a carboxylic acid; the ^{1}H NMR showed only aromatic resonances and was initially uninformative. Titration of the product with a standard base gave a neutralization equivalent of 238, and structure **4** (calculated MW 240) was assigned to this com- pound. Heating **4** led to the known compound imesatin **5**, which was synthesized by the reaction of aniline with isatin[4] and compared to **4**. Thermogravimetric analysis (TGA) of 4 led to a weight loss of 7%, as is expected for the postulated chemistry, which is summarized in Figure 2.
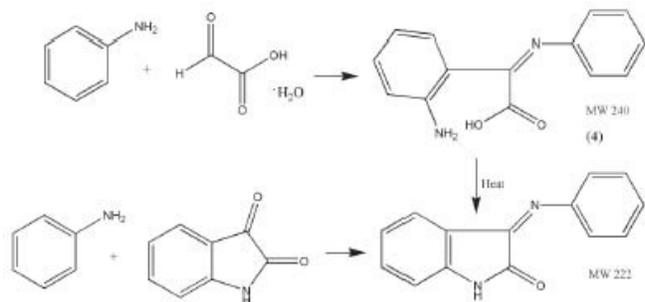
Figure 2: *Formation of imesatin by two routes*

While **2** has not yet been obtained, imesatin has the same chromophore as **2**, albeit in a cyclic array. Accordingly, it was irradiated with a 254 nm uv lamp, but no thermal or uv initiated solid state reactivity was found. A search of the Cambridge Structural Database[5] revealed that the double bonds in the imesatin crystal structure are not oriented for solid state reactivity.

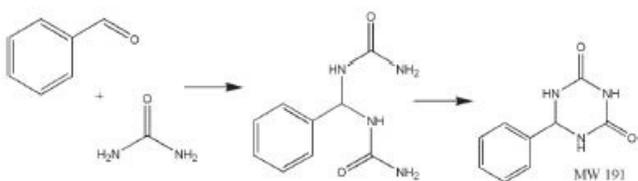## Reaction of Benzaldehyde and Urea

The synthesis of **3** (X= -NH$_2$), benzylidene urea, was reported in the literature. Juaristi[6] refluxed benzaldehyde, urea, and p-toluenesulfonic acid monohydrate in toluene with a Dean-Stark trap to synthesize benzylidene urea, providing reasonable evidence to the structure in the form of IR spectral data, ^{1}H NMR, and ^{13}C NMR.

A synthesis of **3** was attempted by simply heating benzaldehyde and urea in a test tube at 100°C. In identifying the product's melting behavior, it was found that the melt was not reversible, suggesting thermal activity. Differential scanning calorimetry (DSC) confirmed the thermal activity—the endotherm associated with the second heating revealed less heat than that of the initial heating, indicating thermal activity. However, a repetition of this synthesis using freshly distilled benzaldehyde resulted in no reaction occurring. It is believed that the initial reaction was initiated by benzoic acid, a frequent impurity in benzaldehyde, so a few milligrams of that were added. The resulting solid was suspended in hot water, followed by warm acetone to isolate the thermal product. TGA and DSC show that this thermal product is itself thermally reactive, displaying a weight loss above 178°C and a difference in the heat absorbed between subsequent heatings. Following this, a repetition of Juaristi's synthesis was performed. The resulting solid, practically insoluble in numerous solvents, also exhibited thermal reactivity, and TGA and DSC confirmed a decomposition, which is at variance with Juaristi's report. The TGA shows a 5% decrease in weight from 125°C to 169°C, followed by a 75% decrease in weight at 252°C. IR (cm^{-1}): 3434, 3307, 1642, 1595, 1529, 1447, 1366, 1311, 1230, 1200, 1140, 1091, 1053, 1010, 1001, 914, 814, 748, 734, 695, 591, 542, 428. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 5.41 (s), 7.62 (t), 7.73 (t), 7.92 (d). Analysis by electrospray ionization mass spectrometry (ESI-MS) in 0.05% acetic acid indicates the presence of a [M]$^+$ *m/z* of 191.339, which does not suggest that **3** was synthesized. This is illustrated in Figure 3.
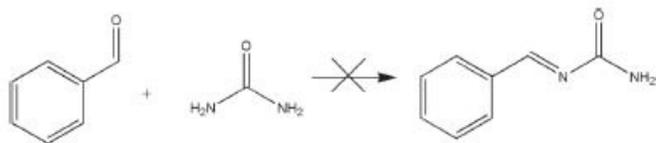
Figure 3: *The unsuccessful synthesis of **3***

Due to the discrepancy between the literature and our experiments, a more comprehensive literature survey into both benzylidene urea and the reaction of benzaldehyde and urea was performed. A paper by Ji[7] was found, which claims that a reaction between p-chlorobenzaldehyde and urea in the presence of p-toluenesulfonic acid in toluene results in the formation of a bisurea, with two equivalents of urea adding to the carbonyl carbon. Also, several papers by Schiff[8] were found, in which he calls the product of the reaction between benzaldehyde and urea benzylidenebiuret. In addition, Das-Gupta[9] reports that benzaldehyde and urea condense to form benzylidenebiuret, which decomposes above 270°C and is practically insoluble in a variety of solvents. A search of *March's Advanced Organic Chemistry* revealed that amides frequently react with aldehydes in the presence of bases or acids to form alkylidene or arylidene bisamides via an acylated amino alcohol[10]. Considering this information, it is possible that benzylidene bisurea was formed to some extent when Juaristi's synthesis was performed—the molecular ion at 191.339 may be the result of a reaction between benzylidene bisurea and acetic acid, resulting in the cyclization of the bisurea and the loss of ammonia, *m/z* calculated for $C_9H_9O_2N_3$ 191.19. This is summarized in Figure 4. Pandey[11] reports a synthesis of benzylidene bisurea, which was repeated for comparison; however, the material obtained was not identical to the product obtained from Juaristi's synthesis in either IR or NMR. At the present time, it cannot be said with absolute certainty that the product obtained from Juaristi's synthesis is one component, which may be the cause of some of these discrepancies.


Figure 4: *Reaction of benzaldehyde and urea to produce the cyclic bisurea.*

Reaction of Thiophene-2-carboxaldehyde and Urea

Another avenue considered was the reaction of thiophene-2-carboxaldehyde and urea. Upon refluxing in toluene with p-toluenesulfonic acid as a catalyst, a tan solid was isolated. Thermogravimetric analysis showed that the product is inconsistent with thiophenylidene urea **5**. On the basis of NMR and MS, the compound is assigned the structure **6**. ^{1}H NMR (DMSO-$_{d_6}$,

400 MHz): δ 5.78 (s, 1H)), 7.01 (t, 1H), 7.08 (s, 1H), 7.53 (t, 1H), 8.28 (s, 2H), 9.46 (s, 1H). ESI-MS: *m/z* calculated for $C_7H_7O_2N_3S$ 197.22, found $[M]^+$ 197.270.
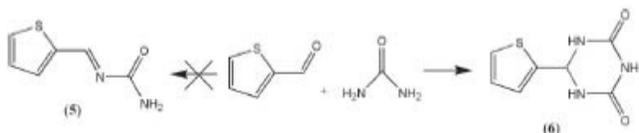
Figure 5: *Reaction of thiophene-2-carboxaldehyde and urea*

Semicarbazones

Another series of compounds with the desired carbon-nitrogen double bond are the semicarbazones, synthesized from the reaction of an aldehyde with semicarbazide hydrochloride in a basic solution[12]. Two semicarbazones were synthesized—benzaldehyde semicarbazone and p-chlorobenzaldehyde semicarbazone, identified by melting temperature and IR spectroscopy. Upon irradiation of the two semicarbazones with a 254 nm uv lamp, it was discovered that there was no apparent change in either melting behavior or in the infrared spectra, indicating the lack of a uv initiated reaction. In addition, the melt was reversible, suggesting that no thermal reaction is taking place either. A search of the Cambridge Structural Database[5] revealed that the double bond of benzaldehyde semicarbazone is not oriented for solid state reactivity.

Further Work

Other avenues of obtaining pure samples of **3** are under consideration. Sahu and Sahu[13] report the synthesis of **3** by using various acidic clays, such as hydrotalcite, an aluminum magnesium hydroxide carbonate hydrate[14], and kaolin, a hydrated aluminum silicate[15]. They offer a reasonable structure proof, including proton and carbon NMR and a molecular ion in the mass spectrum. Repetition of their work would be informative, but the clays have not yet been obtained. Additionally, Lu[16] reports the synthesis of the ethyl ester of **3** using benzaldehyde, urethane, and sodium benzenesulfinate, which may potentially be treated with ammonium hydroxide to yield **3**. A derivative, substituting urea for urethane, may also be attempted to synthesize **3**.

Summary

We have found imesatin and the semicarbazones are unreactive to ultraviolet light for structural reasons. The synthesis of **3** as described by Juaristi is not reproducible. Our efforts to obtain a pure sample of **3** continue.

Acknowledgements

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