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Nucleophilic Behavior of DBU in a Conjugate Addition Reaction

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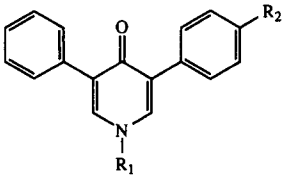
Abstract: Reaction of DBU with a diarylpyrone results in 1,4 addition of the DBU and subsequent fragmentation of the DBU moiety into an aminopropyl caprolactam. Incorporation of the fragmented DBU into the diarylpyridone is postulated to occur by an addition/elimination pathway.

In the course of our studies on the biological activity of pyridones (**1**), we sought a method to rapidly access a large number of analogs. The routes available from the literature[1] generally suffered from some limitations such as low conversions, extensive workups, or incompatible solvents/equipment when adapted to our needs. We thus investigated alterations of the known procedures that would be amenable to our requirements.



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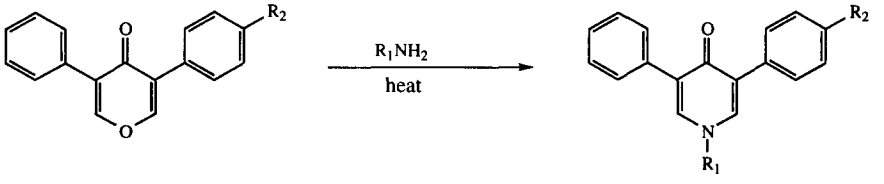
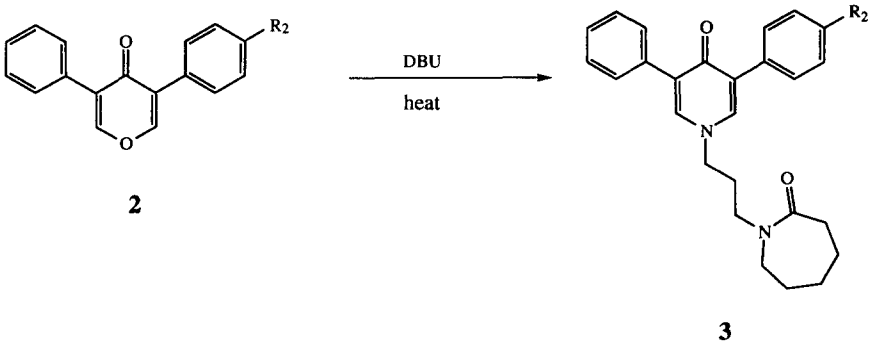
While we were interested in changes in both R_1 and R_2, our initial efforts were directed towards diversity at the pyridone nitrogen. For our needs the most suitable precursor to the pyridones were the pyrones (**2**)[2]. After some experimentation we had good success in the conversion of **2** to the pyridones[3] via the neat reaction between **2** and an amine at ~ 80-130°C (Scheme 1).



2 **1**

Scheme 1

The neat reaction worked well with a wide variety of primary amines, but was generally unsuccessful when the amine was used as its hydrohalide salt. Attempts at *in situ* neutralization of the amine salt by inclusion of typical bases (Et_3N, Hunig's base, K_2CO_3, etc.) with or without other solvents in the reaction mixture met with little success. Addition of DBU, however, gave good yields of the desired pyridones with some amines, but in most cases gave a single compound that appeared to be independent of the amine used. Consequently, with no amine present, exposure of **2** to excess DBU for 3 minutes at 120°C gave a quantitative conversion to the unknown compound. NMR and MS characterization confirmed the structure as the caprolactam pyridone (**3**) (Scheme2).

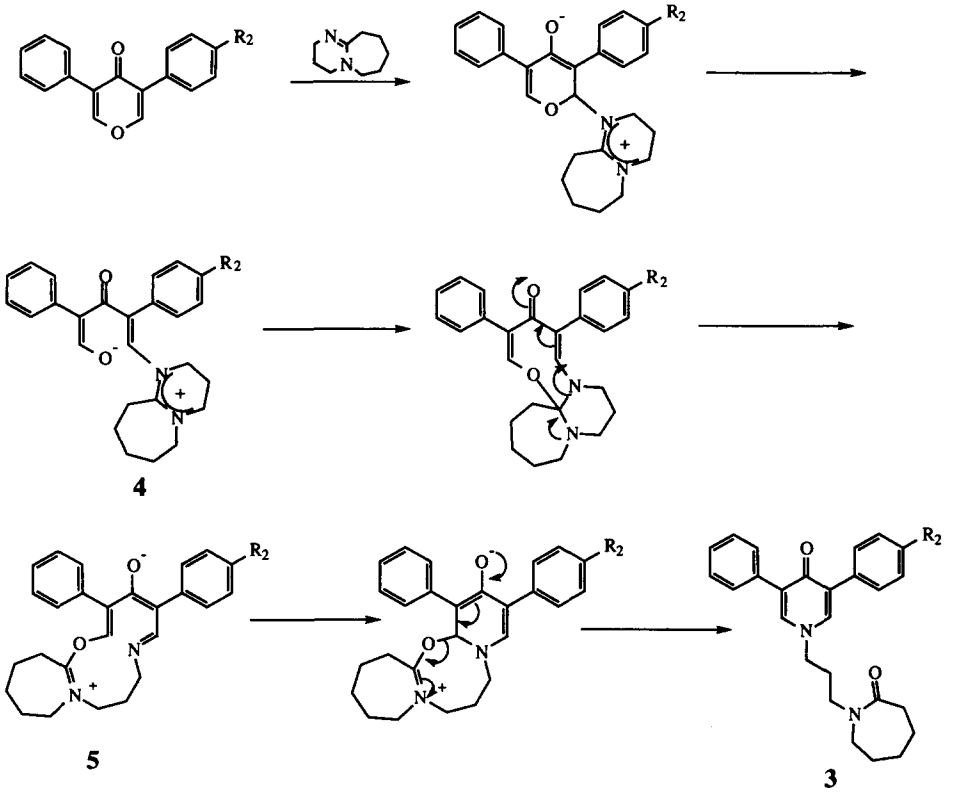


2 **3**

Scheme 2

Examination of the literature reveals only a few instances in which the nucleophilic behavior of DBU is described and products resulting from that behavior have been isolated and characterized[4]. Those products typically are covalent salts between DBU and the substrate during dehydrohalogenation reactions. Of particular importance to our finding was that of Lammers et al[5], who reported modest yields of a caprolactam product in a dehydrohalogenation/alkylationreaction.

In Scheme 3 a mechanism for the formation of **3** is proposed. Initial conjugate addition of the imine nitrogen is followed by retro-Michael addition of the vinylogous carboxylate. After intramolecular trapping of the amidinium intermediate by the vinylogous carboxylate, the DBU ring system fragments to the 12-membered ring **5**. Electrocylic ring closure followed by elimination of the amidate affords the pyridone caprolactam.



Scheme 3

Another plausible mechanism, similar to one proposed by Lammers et al[5], involves trapping of intermediate **4** with adventitous water, fragmentation of the DBU ring system to an amino caprolactam, and then pryidone ring formation by an addition/elimination reaction. In order to obtain evidence for one of these two possible mechanisms we treated the pyrone (**2**) to the usual reaction conditions (DBU/heat) in the presence of 25 equivalents of 95 atom% ^{18}O water. Mass spectral analysis of the resulting pyridone showed only about 7% incorporation of ^{18}O into the caprolactam carbonyl of **3**. This is clear evidence for the intramolecular transfer of the pyrone oxygen into the caprolactam carbonyl postulated in Scheme 3.

To our knowledge the finding reported here is the first example of the isolation and characterization of a product resulting from the conjugate addition of DBU with an α,β unsaturated system[6]. Also intriguing is the speed at which the reaction occurs and the pronounced lack of side products. The details of our general preparation of the pyridone analogs and their biological activity will be reported in due course.

Acknowledgment: We thank Rick Jagdmann, John Lampe, and Yen-shi Lai for helpful discussions and Bernd Soltmann for obtaining the mass spectral data for the compounds presented in this article.

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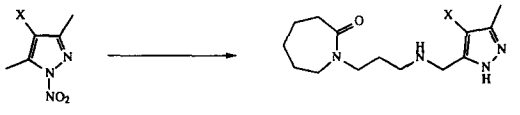

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6. Other workers have investigated the α-alkylations of α,β-unsaturated enones with DBU and DABCO and have concluded that DBU does not catalyze the reaction via a 1,4 addition as is the case with DABCO: Hwu, J. R.; Hakimelahi, G. H.; Chou, C. T. *Tetrahedron Lett.* **1992**, *33*, 6469-6472. b) Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031-2032.

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