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Synthesis of novel indenoquinolines and indenopyridazines via photoisomerization of benzotropolone derivatives

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ABSTRACT

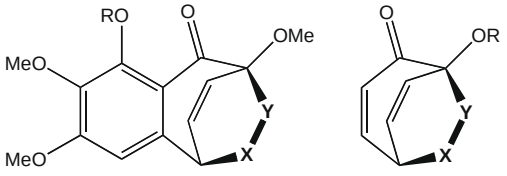
We describe the photoisomerization of hetero Diels–Alder adducts of tetramethylpurpurogallin bearing β,γ-unsaturated ketone chromophores and endocyclic –N–O– or –N–N– groups. Based on spectroscopic and crystallographic data, our results indicate that the outcome of the reaction for the two types of substrates can be correlated with the difference in the stabilities of the radical intermediates generated in each case. For oxazines, the photoisomerization involves both the β,γ-unsaturated ketone and –N–O– moieties, and proceeds through the formation of allyl, benzoyl, phenyl, and α-carbonyl radical intermediates. While the same allylic and benzoyl radicals are formed in adducts with an –N–N– group, the hydrazine does not participate in the reaction and the product is a simple rearrangement of the initial intermediate.

Despite recent efforts, endemic parasitic diseases such as malaria, sleeping sickness, Chagas, and kala azar continue to represent a threat to the population of tropical and sub-tropical regions. Given the adaptability of the causative microbes, new chemotherapies to combat current and future resistant strains are constantly needed.[1] To this effect, we have focused our attention on a series of bridged oxazines and hydrazines obtained by means of a hetero Diels–Alder reaction between benzotropolone and tropolone derivatives and heteroatomic dienophiles (Fig. 1).[2–8]

Several of these compounds have promising biological activity against *Trypanosoma cruzi* and *Leishmania donovani*,[2,3] and their unique structures make them interesting leads in the design of novel antiparasitic agents. In order to further increase the structural diversity of our compound libraries, and given the versatility of this type of hetero Diels–Alder adducts,[9–12] possible modifications of their molecular framework were examined.

Common to all these compounds is a β,γ-unsaturated ketone moiety, a chromophore known to undergo a variety of photochemical transformations.[13] Therefore, and guided partly by the results obtained by Forbes et al. on related β,γ-unsaturated ketone systems,[14–19] we investigated the suitability of photochemical methods for the generation of novel structures. Oxazine **1** and hydrazine **2**, which are representative of benzotropolone derivatives bearing endocyclic –N–O– and –N–N– groups, respectively, were used as models (Fig. 2).

In the case of **1**, a search for reaction conditions revealed that irradiation in either benzene or methanol solution using borosilicate or soda-lime glass reactors resulted in the formation of a single product. The highest yields were obtained when irradiations were carried out in benzene solution and a soda-lime glass reactor was employed (see Supplementary data for details). Following chromatographic purification, high resolution MS showed that the molecular formula of the new compound was identical to that of **1**, indicating that a photoinduced isomerization had taken place. In the IR spectrum, strong absorption bands at 3414, 1737, and 1701 cm^{-1} revealed the likely presence of primary amine, cyclopentanone, and ester functionalities, respectively. Part of this information suggested that cleavage of the –N–O– bond had taken place. This was confirmed following detailed interpretation of 1D and 2D (COSY, HMQC, and HMBC) ^{1}H and ^{13}C NMR data, which allowed us to elucidate the structure of the photoisomer as that of indenoquinoline **3** (Fig. 3).[20] In particular, long-range correlations between H-9 and C-5a and from H-10 to C-9a and C-9 indicated



X = N-Ph, **Y** = O; **X** = **Y** = N-CO_2R' **X** = **Y** = N-CO_2R'

Figure 1. Structure of bridged oxazines and hydrazines with antiparasitic activity.

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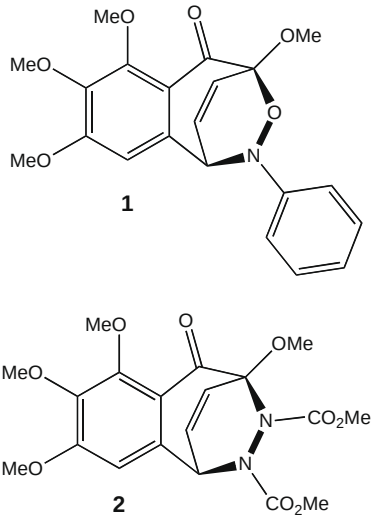


Figure 2. Benzotropolone derivatives bearing endozyclic –N–O– and –N–N– bonds used as models in the studies.

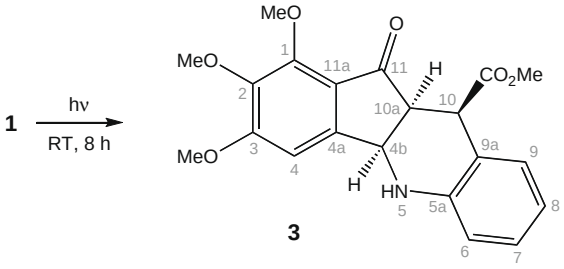


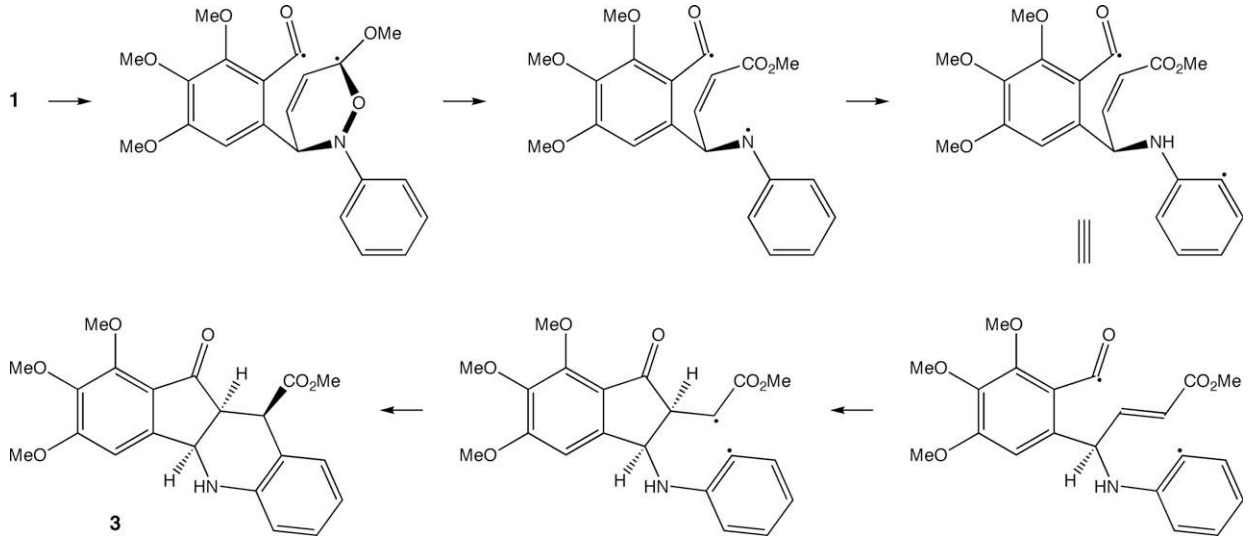
Figure 3. Structure and numbering of indenoquinoline **3**.[20]

clearly that the phenyl group had become part of a fused ring system. Similarly, an HMBC from the carbonyl carbon resonance at 171.2 ppm to the H-10 proton and the methyl protons at 3.48 ppm confirmed the presence of a carbomethoxy group attached to C-10. The relative stereochemistry of the C-4b, C-10a, and C-10 chiral centers was established by analysis of the $^{3}J_{H4b-H10a}$ and $^{3}J_{H10a-H10}$ coupling constants, and revealed a *cis* fusion of the indanone and quinoline fragments and a synperiplanar arrangement of the H-10a and H-10 protons.

Based on this structure and that of the starting material it is possible to explain the photoisomerization process mechanistically. As depicted in Scheme 1, the reaction is initiated by the formation of allyl and benzoyl radicals.[13] This is followed by homolytic cleavage of the –N–O– bond and recombination of the resulting O-centered and allyl radicals to form the methyl ester group anchored at C-10. The N-centered radical then abstracts an aromatic proton to form the secondary amine and a phenyl radical. The benzoyl radical subsequently attacks the olefin from the *re*-face, leading to the formation of the indanone fragment and an α-carbonyl radical. Lastly, the phenyl and α-carbonyl radicals combine to form **3**. It is worth noting that all intermediates in the proposed mechanism are stabilized by delocalization. Furthermore, one chiral center is lost and two new ones are created stereospecifically in the process.

A similar approach was followed with **2**. Although some of the reaction conditions investigated resulted in decomposition of the starting material and the formation of complex mixtures, irradiation of benzene or methanolic solutions of **2** in borosilicate or soda-lime glass reactors, respectively, led to the formation of a single product in yields ranging from 16 to 27% (see Supplementary data). As was the case for **1**, high resolution MS of the purified material showed that a photoisomerization had taken place. The IR spectrum had a prominent carbonyl signal at 1746 cm^{-1}, which could as before be attributed to a cyclopentanone moiety. In addition, the presence of a carbonyl signal at 1712 cm^{-1} and the absence of an N–H stretching band suggested that the carbamate groups and the –N–N– bond had remained intact. The former was supported by the fact that several signals in the ^{1}H NMR spectrum were broadened, a phenomenon which is commonly observed with molecules bearing carbamate moieties.[3] Careful interpretation of the 1D and 2D NMR data allowed us to determine the structure of the photoreaction product as indenopyridazine **4** (Fig. 4a). This was further supported by low-resolution X-ray diffraction studies which yielded a 3D structure of **4** in agreement with our initial assignments (Fig. 4b).

Contrary to what was observed for **1**, formation of **4** does not involve the hydrazo group present in the starting material. In this case the process is a simple rearrangement in which the allyl and benzoyl radicals formed initially recombine following a 1,3-shift (Scheme 2). The differences in photoreactivity between **1** and **2**



Scheme 1. Proposed mechanism for the photochemical isomerization of **1** into indenoquinoline **3**.

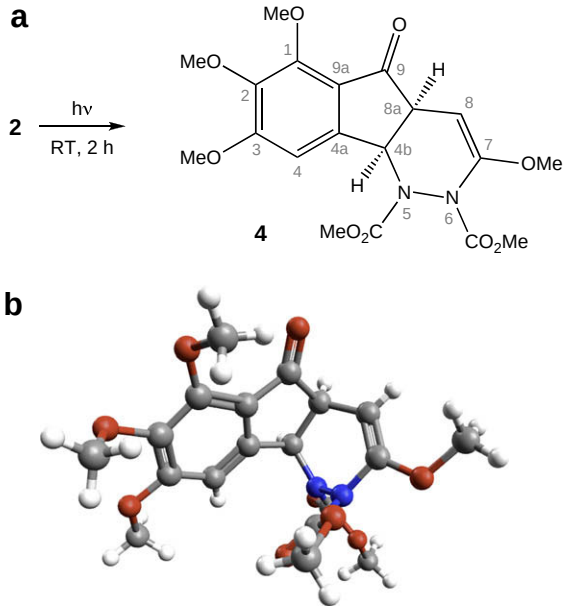


Figure 4. Structure and numbering of indenopyridazine **4** (a), and 3D structure based on low-resolution X-ray diffraction data (b).

can be explained by comparing the stabilities of the intermediates generated in each case. As noted above, all radicals that participate in the conversion of **1** to **3** following the homolysis of the oxazine can participate in resonance. On the other hand, cleavage of the –N–N– bond in **2** would lead to the formation of unstable intermediates.

The results presented in this Letter show that benzotropolone derivatives bearing β,γ-unsaturated ketones can be easily converted into novel compounds by means of photochemical transformations. As expected, our data reveals that despite being initiated through the same chromophore, the outcome of the reactions depends on the stability of various intermediates. This suggests that the structure of the products could, in principle, be controlled by selection of the functionalities present in the starting materials. For example, preliminary results indicate that the application of this strategy to tropolone derivatives with analogous β,γ-unsaturated ketone moieties leads to completely different molecular frameworks than the ones reported here. The findings from these ongoing studies, as well as the biological evaluation of these novel compounds, will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.176.

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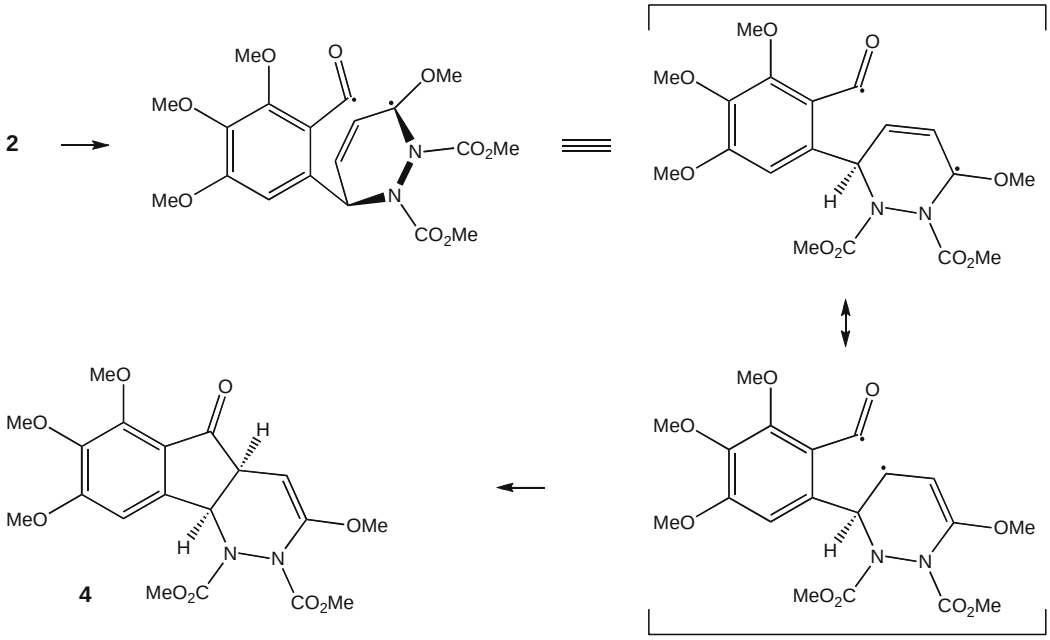

Scheme 2. Proposed mechanism for the photochemical isomerization of **2** into indenopyridazine **4**.

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