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Dimerization and comments on the reactivity of homophthalic anhydride

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This paper is respectfully dedicated to the late Professor Harry H. Wasserman, an inspiration to chemists young and old

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ABSTRACT

Homophthalic anhydride (HPA) dimerizes under the influence of base to provide, sequentially, the (3–4′)-C-acyl dimer, a pair of chiral diastereomeric bis(lactones), 3-(2-carboxybenzyl)isocoumarin-4-carboxylic acid, and finally, 3-(2-carboxybenzyl)isocoumarin. The structures of the bis(lactones) were misassigned in 1970 based on the (presumed) *cis* thermal decarboxylative elimination reaction of the lower melting one. The preferred pathway should be *trans–anti*, however, and crystallographic analysis of one of the bis(lactones) reverses the earlier assignment. The formal cycloaddition reaction of HPA with imines occurs in preference to HPA dimerization; the mechanistic implications of this reactivity difference are discussed.

Introduction

New antimalarials continue to be a first line of defense against infection by the *Plasmodium* agent and its ability to develop resistance to even highly effective older drugs such as those based on artemisinin.[1] We recently developed a new class of antimalarial agents based on the 1,2,3,4-tetrahydro-1-isoquinolone 4-carboxanilide framework.[2] The synthesis of this ring system depends on the formal cycloaddition reaction of imines such as **2** with homophthalic anhydride (HPA, **1**).[3] This reaction is facilitated by *N*-methylimidazole (NMI), and evidence has been presented that the role of NMI is to intercept the putative Mannich intermediate and promote ring closure, while suppressing Knoevenagel-type elimination.[4] Because HPA is known to dimerize under the influence of base,[5,6] and because this latter process would detract from the efficiency of the desired conversion, it was prudent to examine the control reaction in which the imine is not present. We report the results of that experiment, as well as a re-assignment of the stereochemistry of two of the reported HPA dimeric products. Furthermore, the mechanism of our NMI-promoted HPA-imine formal cycloaddition can now be clarified based on observations of the behavior of HPA in the control (imine-free) reaction.

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Results and discussion

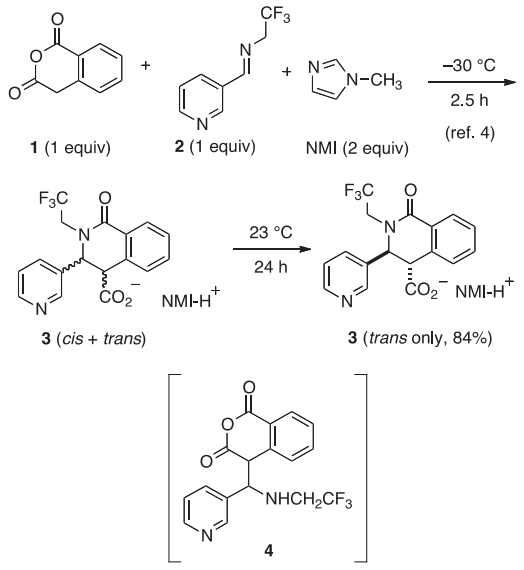
The NMI promoted reaction of HPA with imines

Addition of 2 equiv of NMI to the reaction of certain imines (e.g., **2**, Scheme 1) with HPA (**1**) improves both the yield and selectivity of the reaction.[4] One explanation for the role of NMI is that it intercepts an intermediate Mannich-type amino-anhydride **4**, and thereby promotes the *N*-cyclization process leading to lactam (here, **3**) at the expense of a yield-reducing Knoevenagel-type elimination from **4**. However, for optimization of the imine reaction it was important to establish that parallel reaction of **1** with NMI does not lead to side products that remove **1** from the desired pathway.

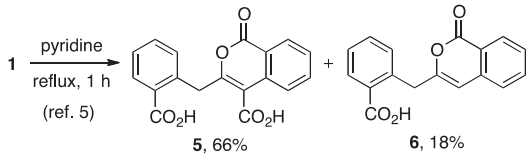
Dimerization reactions of HPA

HPA (**1**) has been reported to undergo dimerization when treated with base. Bogdanov et al.[5] described the isocoumarin derivatives **5** and **6** (Scheme 2) that resulted from heating HPA (**1**) in pyridine solution for 1 h (**5** is the major product) or 3 h (**6** is the major product). Analogous reactions of benzo-substituted HPA derivatives have also been reported.[7,8]

Schnekenburger and Kaiser[6] reported that, under much milder conditions (triethylamine, −15 °C), HPA (**1**) dimerizes to give, after

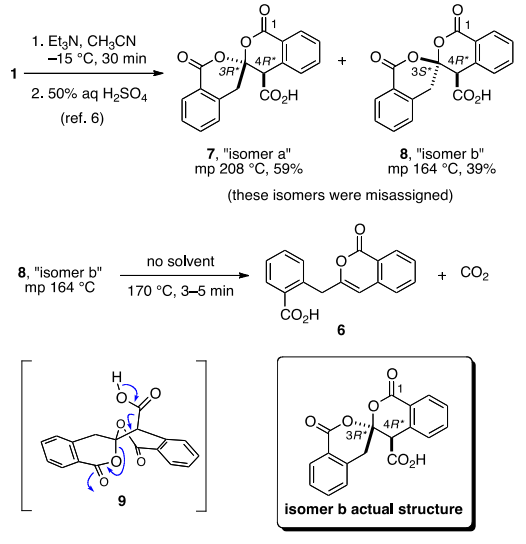


Scheme 1. NMI promoted formal cycloaddition of HPA (**1**) with (*E*)-2,2,2-trifluoro-*N*-(pyridine-3-ylmethylene)ethanamine, **2**.



Scheme 2. Dimeric HPA products at higher temperature.

acid quench, a pair of diastereomeric bis(lactones) **7** and **8** (Scheme 3). The lower melting isomer was assigned the (3*S**,4*R**) structure **8** (arbitrary HPA numbering, 'isomer b') based on its thermal decarboxylative elimination to give **6**. The assumption was made that this is a *cis*-elimination. However, ample literature precedent[9–11] suggests that, in a decarboxylative elimination, the departing heteroatom (here, the lactone ring carboxylate oxygen atom, as shown in **9**) is aligned most favorably in a *trans–anti* arrangement with respect to the breaking carbon-carbon bond to CO_2. Only the (3*R**,4*R**) bis(lactone) can achieve this geometry



Scheme 3. Bis(lactone) dimeric HPA products at lower temperature and (mis)assignment of their structures.

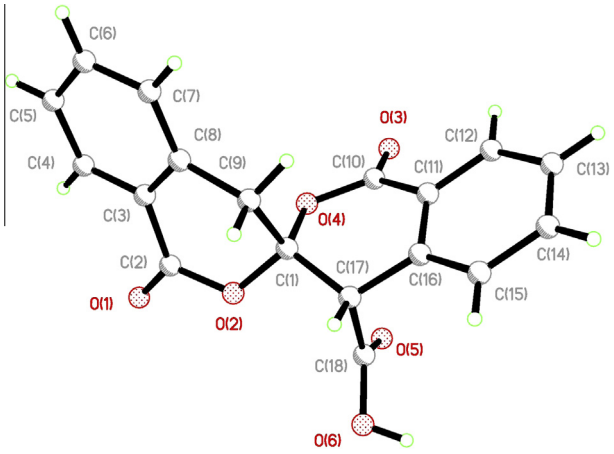


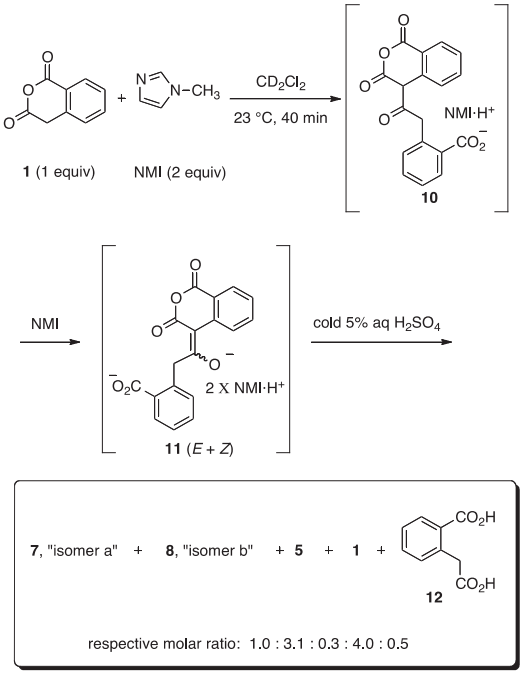
Figure 1. ORTEP representation of higher melting 'isomer a'.

(namely, **9**), suggesting that the actual structure of 'isomer b' is that shown in the box (Scheme 3).

By following the procedures shown in Schemes 2 and 3, we have synthesized authentic samples of HPA dimers **5**, **6**, **7**, and **8**. Crystals of the higher melting 'isomer a' (initially assigned as **7**), obtained by slow evaporation of a solution in propionitrile, were analyzed by X-ray crystallography. The actual structure of 'isomer a' (see ORTEP representation, Fig. 1) was thereby shown to possess the 3*R**,4*S** stereochemistry, with the CO_2 and lactone ring O substituents *cis*. The actual structure of 'isomer b' must be 3*R**,4*R** (Scheme 3, in box), with the CO_2 and lactone ring O substituents *trans*, in harmony with its decarboxylative elimination reaction to give **6**.

The control reaction of HPA with NMI

The reaction of HPA (**1**, 1 equiv) with NMI (2 equiv) in dichloromethane-d_2 solution, equivalent to conditions under which **1** reacts rapidly with **2**,[4] was monitored by ^{1}H NMR spectroscopy (Scheme 4). After 2 min, small amounts of **7** and **8** were apparent,



Scheme 4. Reaction of HPA with NMI in dichloromethane solution.