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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7809–7812

Amine-catalyzed epimerization of γ-hydroxybutenolides

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Received 20 June 2007; revised 2 September 2007; accepted 4 September 2007
Available online 8 September 2007

Abstract—The amine-catalyzed epimerization of chiral γ-hydroxybutenolides leads to a fast exchange on the NMR time scale.

The γ-hydroxybutenolide moiety (5-hydroxy-2(5*H*)-furanone) appears in a number of pharmacologically active natural and unnatural products.[1–18] The diverse biological activity of manoalide (Fig. 1), dysidiolide, and many other naturally occurring γ-hydroxybutenolides has prompted numerous synthetic investigations.[19–21] The γ-hydroxybutenolide moiety has been established as the important pharmacophore for many of the biologically active γ-hydroxybutenolides.[22]

The experimental evidence suggests that γ-hydroxybutenolides are in dynamic equilibrium with the open-chain tautomer, the corresponding 4-oxo-2(*Z*)-alkenoic acid form.[23–31] The equilibrium for the ring-chain tautomerism for simple 4-substituted-5-hydroxy-2(5*H*)-furanones largely favors the ring tautomer. Since many naturally occurring γ-hydroxybutenolides contain additional chiral centers, the compounds are usually represented as a pair of epimers at the C-5 carbon. In many cases, a mixture of epimers is apparent in the ^{1}H and ^{13}C NMR, with either a clear set of 'doubled' peaks for protons and carbons at or near the C-5 chiral center (indicating slow exchange),[1–9] or with broad and poorly defined peaks (indicating intermediate exchange).[2,10–13]

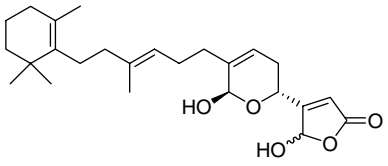
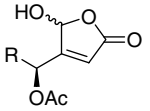


Figure 1. Manoalide.

Although a number of chiral γ-hydroxybutenolides appear to have a sharp sets of peaks in the proton and carbon NMR in some solvents,[13,32] most authors represent the C-5 center as epimeric, in recognition of the likelihood of fast exchange on the laboratory time scale between the two epimers in solution. In some cases, however, conformational constraints significantly favor one epimer over the other.[14,15,29] Further, as in the case of dysidiolide,[2] selective crystallization of one epimer is possible.

The recent report by Patil and Liu[33] challenges the view of fast epimerization on the laboratory time scale for chiral γ-hydroxybutenolides. In their study, singlet oxygen oxidation of furans prepared by the Baylis–Hillman reactions of 3-furaldehyde is reported to give either an epimeric pair of γ-hydroxybutenolides using NEt_3 as a base or a single epimer using Hünig's base. The proposed stability of a C-5 epimeric center is not unprecedented,[34] but appears to be at odds with most of the literature and some of our recent work, too. This Letter describes some of our initial studies exploring the catalysis of the epimerization process of manoalide and the related racemic 4-substituted-5-hydroxy-2(5*H*)-furanones **1** (Fig. 2), and a reexamination of the study of Patil and Liu.[33]



1a; R=$(CH_2)_5C_6H_5$ (AGN-190576)
1b; R=$(CH_2)_{11}CH_3$ (AGN-190383)

Figure 2. 4-Substituted-5-hydroxy-2(5*H*)-furanones **1**.

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0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.09.017

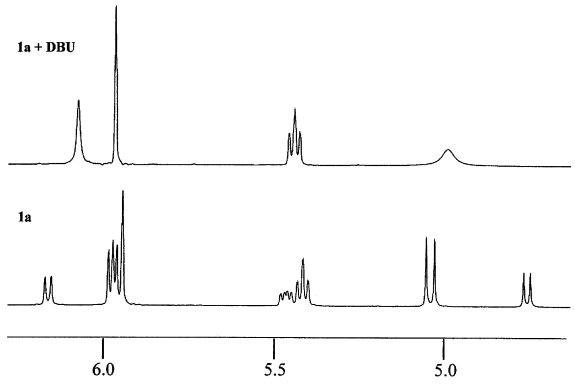


Figure 3. Partial ^{1}H NMRs of **1a** (0.10 M in $CDCl_3$) with DBU (0.5 mol %) and untreated **1a**.

We have found that amines act as a catalyst in the epimerization of the C-5 position of γ-hydroxybutenolides, although the isomerization of the γ-hydroxybutenolides to 4-oxo-2(*E*)-alkenoic acids was a potential problem.[35] The NMR for **1a** (0.1 M in $CDCl_3$) has two well-defined set of peaks for the two epimers in a 2:1 ratio (Fig. 3). The addition of pyridine (100 mol %) or 2,6-lutidine lead to broad, coalescing peaks. With the addition of DMAP, *N*-methylmorpholine, DABCO, DBU, triethylamine, and hexamethylenetetraamine (0.5 mol %), the peaks coalesced into sharper signals, representing a weighted average of the two epimers (with the incidental loss of observable coupling between the hydroxy proton and the C-5 proton) and, in the case of the more basic amines such as DBU, a significant contribution from the open-chain carboxylate (vide infra). DABCO was particularly attractive as a catalyst since DABCO has only one signal in the ^{1}H and ^{13}C NMR. The amine-catalyzed epimerization of **1b** proceeded in the same manner as **1a**. The addition of *N*-methylmorpholine or DABCO (2 mol %) to manoalide (Fig. 4) gave a single set of protons and carbons, reflecting the rapid epimerization of the γ-hydroxybutenolide center on the NMR time scale and also the preference for one epimer of the hemiacetal center of the dihydropyranyl ring due to the anomeric effect.[36] The addition of DABCO to an epimeric mixture of *seco*-manoalide gave comparable results.

In addition to examining the epimerization of chiral γ-hydroxybutenolides, we also examined two closely related systems. The addition of DABCO (5 mol %), *N*-methylmorpholine, or DBU led to the coalescence of the diastereotopic methyl protons and carbons in 5-hydroxy-4-(1-methylethyl)-2(5*H*)-furanone **2** (Fig. 5).[37] We also looked at the related tautomerism of 2-acetylbenzoic acid (**3**), which exists in solution as a 9:1 mixture of the ring:chain tautomers.[29,30] The addition of DABCO (5 mol %) to **3** led to the collapse of the proton signals to a weighted average of the two tautomers.

In light of our results, we reexamined the work of Patil and Liu,[33] preparing γ-hydroxybutenolide **4** (Fig. 6). We were able to isolate **4** as a mixture of epimers (1:1) with a ^{1}H and ^{13}C NMR spectra similar to the reported spectra.[33,38] The addition of various amines to **4** leads to the coalescence of the two epimers in NMR spectra to a single set of peaks. We have found that as little as 0.3 mol % of Hünig's base (a possible impurity in the synthesis of **4**) catalyzes the epimerization process to give NMR spectra that are an average of the two epimers. These NMR spectra were nearly identical to the NMR spectra reported for the proposed pure *syn*-epimer of **4**.[33] When TsOH is added to this solution of **4** containing Hünig's base in $CDCl_3$, the two epimers appear again as well-resolved set of peaks. We hypothesize that the incomplete removal of Hünig's base is responsible for the catalysis of the epimerization process and the appearance of a single set of peaks in the ^{1}H and ^{13}C NMR spectra for the compound identified as the *syn*-epimer of **4**. Further, we believe the appearance of two epimers in unpurified (acidic) $CDCl_3$ is the result of protonation of the amine impurity and subsequent slow exchange on the NMR time scale between the two epimers of **4**, rather than the proposed acid-catalyzed epimerization of the pure *syn*-epimer of **4** by the presumptive HCl.

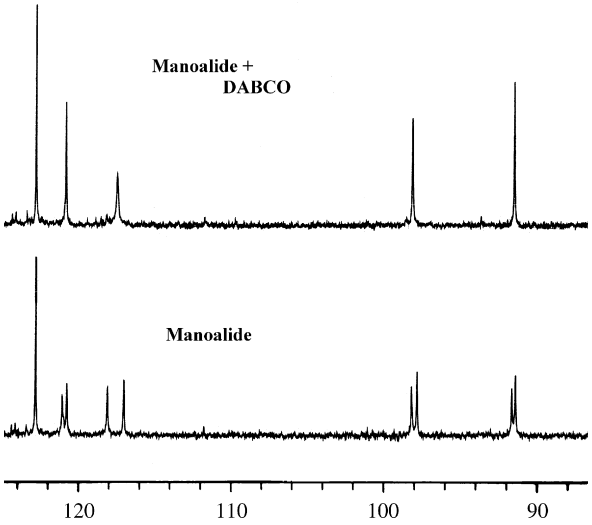


Figure 4. Partial ^{13}C NMR of manoalide (0.10 M in $CDCl_3$) with DABCO (2 mol %) and untreated manaolide.

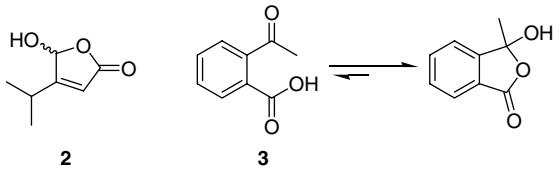


Figure 5. 5-Hydroxy-4-(1-methylethyl)-2(5*H*)-furanone (**2**) and 2-acetylbenzoic acid.

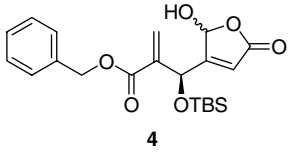
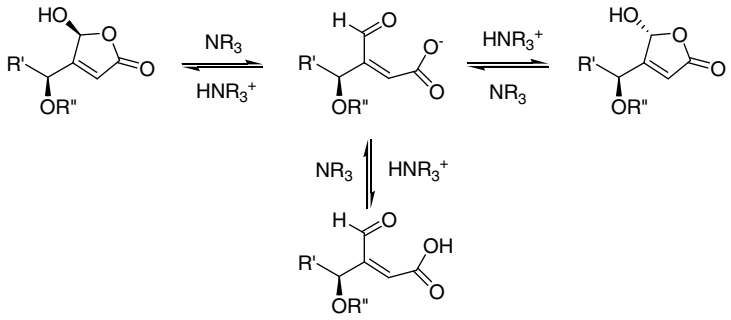


Figure 6. γ-Hydroxybutenolide **4** from Ref. 33.



Scheme 1. Mechanism for the amine-catalyzed epimerization of γ-hydroxybutenolides.

The careful mechanistic studies by McClelland[25] and Bowden[26,27] provide an excellent starting point for the proposed amine-catalyzed epimerization of γ-hydroxybutenolides presented in Scheme 1. With more basic amines such as DBU and Hünig's base, the open-chain carboxylate will also contribute to the weighted average of the protons and carbons in the NMR spectra.[39] Qualitatively, the rate of epimerization appears to be related to the basicity of the amines (C_5H_5N < NMM < DBU), but much more careful rate studies will be necessary before making any quantitative statements.

The amine-catalyzed epimerization of γ-hydroxybutenolides offers a means of simplifying the NMR spectra of complex chiral γ-hydroxybutenolides that are at slow or intermediate rates of exchange on the NMR time scale, facilitating the identification of these compounds.[40] Although the isomerization of the γ-hydroxybutenolides to 4-oxo-2(*E*)-alkenoic acids is a potential problem, careful addition of the amine to the γ-hydroxybutenolides avoids this difficulty. This study further underscores the probable rapidness of the epimerization process on the laboratory time scale and the caution one must exercise in assuming a single set of NMR peaks corresponds to a single pure epimer. We are continuing to look at the epimerization process of differently substituted γ-hydroxybutenolides[41] and attempting to quantitatively determine the rates of the amine-catalyzed epimerization process.

Acknowledgments

We thank Professor Liu for her helpful discussions. We are deeply indebted to Drs. Michael Garst and Elizabeth Syage of Allergan, Inc. for their helpful discussions and for the gift of manoalide, *seco*-manoalide, AGN 190383, and AGN 190576. We thank the Petroleum Research Foundation, administered by the American Chemical Society, and Lafayette College's Academic Research Committee for financial support. We gratefully acknowledge a grant from the Kresge Foundation for the purchase of a 400 MHz NMR spectrometer.

Supplementary data

^1H and ^{13}C NMR spectra of the amine-catalyzed epimerization studies of **1**, **2**–**4**, manoalide, and *seco*-manoalide. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.017.

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32. In examining the literature, there is no clear picture of solvent effects in the NMR studies of chiral γ-hydroxybutenolides. In our studies, we used unpurified $CDCl_3$, which contains a trace of HCl, to observe the two epimers of **1**, **4**, and manoalide. These results are in contrast to the studies in Ref. 3, in which epimeric γ-hydroxybutenolides in purified $CDCl_3$ were at an intermediate exchange and in acidic $CDCl_3$ were at fast rate of exchange in the NMR.
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38. The proton and carbon NMR spectra of **4** are concentration dependant, which renders the comparison of NMR spectra of dissimilar concentrations misleading and inappropriate. By carefully adjusting the concentration of the mixture of the epimers of **4**, however, we obtained a ^{13}C NMR spectrum with peaks that differed by less than 0.1 ppm (except for one set of carbons) from the spectrum reported in Ref. 33.
39. With the addition of an equimolar amount of amine (NEt_3 or Hünig's base) to **4**, Professor Liu (Ref. 33) provided good evidence for the generation of the fully formed open-chain carboxylate. When we add amines that are weaker bases (*N*-methylmorpholine or DABCO) in excess of what is needed for fast exchange of the epimers (10–25 mol %), there is not a significant change in the NMR spectra of the epimers of **1** or **4** at fast exchange, indicating the formation of only a small quantity of the open-chain carboxylate.
40. The frustration in determining the structure of dysidiolide was clearly evident in Ref. 2. For the ^{13}C NMR of dysidiolide, some of the peaks 'were hardly visible over the noise level' and there were doubled peaks in the ^{1}H NMR for the hydroxy methine and hydroxyl protons as well as for a number of carbons in the ^{13}C NMR. The authors stated that 'since no unequivocal structure could be determined from these data', X-ray studies were undertaken. The authors also noted, however, that the proximity of the arms of dysidiolide may lead to hindered motions and hence the multiple peaks in the NMR. Since some of the NMR spectra of dysidiolide in subsequent synthetic studies have sharper peaks in the NMR, we suspect that impurities (or a lower concentration of HCl) in the NMR solvent are catalyzing the epimerization process.
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