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Acid-Catalyzed Rearrangement of Fused Alkylideneoxetanols

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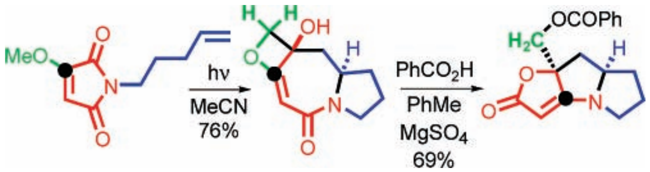
ABSTRACT



Complex aza-fused tricyclic lactones are obtained in a two-step photochemical cycloaddition/acid-catalyzed rearrangement of simple alkoxy maleimide derivatives. The sequence involves a complex acid-catalyzed skeletal rearrangement of the intermediate alkylideneoxetanols.

Although less prevalent than the ubiquitous nucleophilic ring-opening of epoxides, the equivalent reaction of the four-membered oxetane ring system has served as a useful methodology in synthesis.[1] The use of substituted oxetanols allows access to a range of diastereomerically pure 1,2-diols as demonstrated by the extensive studies of Bach et al.[2] The overall strategy is rendered synthetically useful by virtue of easy access to a range of oxetanes via the photochemically mediated Paternò−Büchi reaction.[3] Other routes to substituted oxetanes have included the photochemical Norrish II reactions of α-alkoxy ketones.[4] A particularly striking example of this was reported by Feigenbaum and Pete who demonstrated that very strained alkylideneoxetanols could be synthesized by irradiation of steroidal derived α-alkoxy enones.[5]

Previously we reported the [5 + 2] photocycloaddition of *N*-pentenyl-substituted maleimide derivatives as a convenient and very rapid method for the synthesis of fused azepine ring systems.[6] More recently, alkoxy-substituted maleimides such as **1** have been found to undergo a cascade sequence of [5 + 2] cycloaddition followed by a Norrish II cyclization of the major initial cycloadduct **2**. Overall this provides an expeditious route to complex azepine-fused alkylideneoxetanols such as **3** in a single photochemical operation from alkoxymaleimides (Scheme 1).[7]

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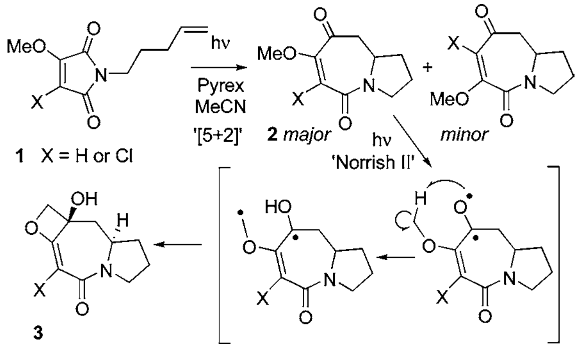
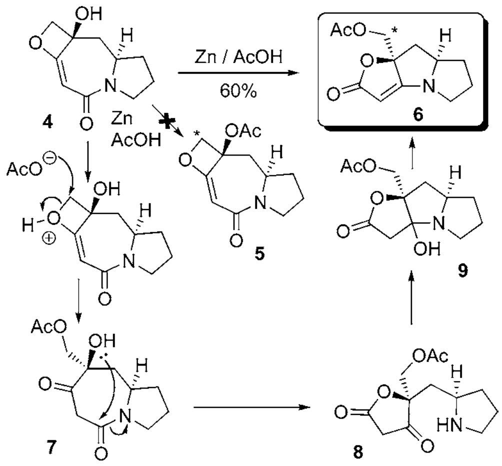
Scheme 1. Maleimide [5 + 2] Cycloaddition/Norrish II Cascades[7]



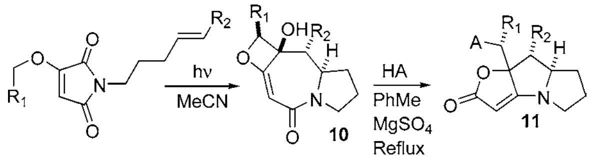
Upon investigating the further reactivity of oxetane derivatives such as **4** (Scheme 2) unusual reactivity was observed.

Scheme 2. Acid-Catalyzed Rearrangement of Alkylideneoxetanols



The azepine [5 + 2] photoproducts derived from dichloromaleimides can generally be reduced/dechlorinated to the fully saturated azepines[6a] using Zn/AcOH. Application of the usual Zn reductive protocol to **4** gave a product that was found to incorporate an acetate group and was initially proposed to be the simple acetate ester **5** (Scheme 2). However, after further detailed analysis subtle but important spectral inconsistencies revealed this structure to be untenable. Although almost identical in every respect to previous azepine−oxetanols (H/C multiplicities, chemical shifts), the observed coupling constants for the diastereotopic protons indicated (*) were found to be ^2J = 11.7 Hz. This was significantly different from the oxetane couplings observed in systems such as **3** (usually of the order of 6 Hz). After further detailed analysis the new structure **6** was proposed which was clearly the result of a significant acid-catalyzed rearrangement. It was soon found that the Zn played no role in the reaction and variation of the acid allowed incorporation of different groups (Table 1). While initial reactions based on the reduction conditions used acetic acid as solvent, this excess of acid was found to be unnecessary. Simple reflux in toluene with the appropriate acid (1.5 equiv) was all that was necessary to precipitate the rearrangement sequence. The use of 3-nitrobenzoic acid (Table 1, entry 4) led to the crystalline product **11** (R_1 = H, R_2 = H, A = 3-$NO_2C_6H_4CO_2$), which was analyzed by X-ray crystallography (Figure 1) enabling confirmation of the structure of the rearranged skeleton.

Table 1. Rearrangement of Oxetanes[a]



entry	R_1	R_2	**10** yield [%]	acid (HA)	**11** yield [%]	dr[b]
1	H	H	76[c]	AcOH	59	1:0
2	H	H		$PhCO_2H$	54	1:0
3	H	H		$PhCH_2CO_2H$	69	1:0
4	H	H		m-$NO_2C_6H_4CO_2H$	52	1:0
5	H	H		TsOH	47	1:0
6	H	Me	71[c]	AcOH	59	1:0
7	H	Me		$PhCO_2H$	41	1:0
8	Me	H	55[d]	AcOH	47	4:1
9	Me	H		$PhCO_2H$	38	3.5:1
10	Me	H		m-$NO_2C_6H_4CO_2H$	56	3.6:1
11	Me	Me	46[d]	AcOH	34	2.1:1[e]
12	Me	Me		$PhCO_2H$	0	−

[a] Rearrangements typically on a 50-mg scale. [b] Determined by ^1H NMR analysis. [c] Isolated yields by column chromatography. [d] Recrystallized yields of a single diastereomer. [e] Only two diastereomers observed (at the R_1 stereogenic center).

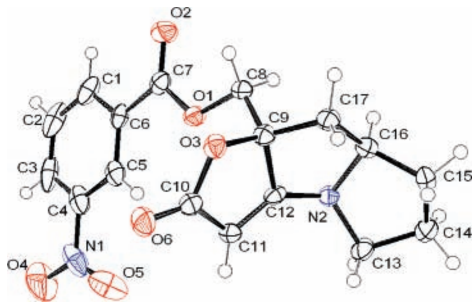


Figure 1. ORTEP representation of **11** (R_1 = H, R_2 = H, A = 3-$NO_2C_6H_4CO_2$).

The rearrangement reaction is proposed to proceed via nucleophilic ring-opening of the oxetane ring, followed by transannular amide cleavage. The ease of ring-opening can

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be rationalized on the basis of relief of strain and the low pK_a of the resulting β-dicarbonyl carbon acid **7**. The resulting amine **8** cyclizes onto the more electrophilic ketone carbonyl to give the aminol **9**, which then undergoes elimination of water to **6** (Scheme 2). It was suggested that removal of water from the reaction mixtures would mitigate the likelihood of reversibility in the later stages of this sequence. To this end a number of standard techniques were investigated (molecular sieves, Dean−Stark), but ultimately it was found that the addition of magnesium sulfate to reaction mixtures significantly increased yields by 10−15%.

To further investigate the rearrangement reaction a number of substituted oxetanol systems were prepared using the same maleimide [5 + 2]/Norrish II cascade sequence previously reported. The continuous flow reactor previously developed by us[8] allowed easy access to gram quantities of these oxetanes. In all cases acid-catalyzed rearrangement of the substituted oxetanes provided the expected rearranged tricyclic lactone products (Table 1).

The stereochemistry was determined by either NOE experiments (entries 6−7 and 11, 12) or X-ray crystallography. Mixtures of diastereomers of **11** were obtained in cases where the oxetane ring bears a stereogenic center (entries 8−12). X-ray crystallography of **11** (R_1 = Me, R_2 = H, A = 3-$NO_2C_6H_4CO_2$) showed the stereochemistry of the major product corresponded to inversion of the reaction center as depicted in Figure 2. This indicates that the initial ring-opening step proceeds mainly via an S_N2 mechanism and that the minor diastereoisomer may possibly originate from a competing S_N1 pathway via the corresponding secondary cation (vide infra). Attempted ring-opening with water using catalytic *p*-toluenesulfonic acid resulted in an interesting product that appeared to incorporate a tosyl group. Use of stoichiometric *p*-TSA allowed isolation of the rearranged product incorporating the TsO moiety (Table 1, entry 5; R_1 = H, R_2 = H, A = OTs).

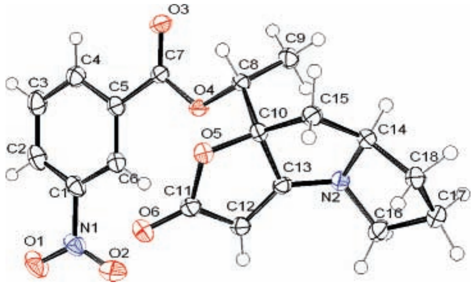
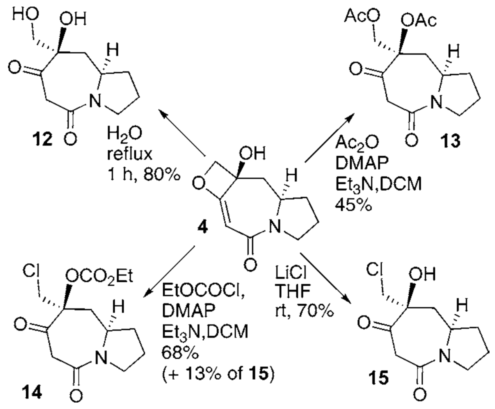


Figure 2. ORTEP representation of **11** (R_1 = Me, R_2 = H, A = 3-$NO_2C_6H_4CO_2$).

During work to confirm the structure of the rearranged products, attempts were made to isolate the initial oxetane ring-opened compound (cf. **7**) by investigating a number of alternative nucleophiles under milder conditions. Simply heating **4** in water resulted in the isolation of the diol **12** in excellent yield, thus confirming oxetane ring-opening as the initial step. Reaction with acetic anhydride in the presence of DMAP gave rise to the diacetate **13** via ring-opening with acetate with concomitant trapping of the intermediate alcohol by acetylation. Use of ethyl chloroformate resulted in a product, **14**, in which chloride displaced by initial acylation of DMAP opens the oxetane ring. In reactions lacking DMAP the oxetane was recovered completely unreacted. Similar reactivity has recently been observed in azetidine systems,[9] albeit without the need for a nucleophilic catalyst. Most surprising was the ease of ring-opening when the oxetane was reacted with LiCl where the chloride anion was sufficiently nucleophilic to open the ring and form the stable halohydrin **15**, previously identified as a minor product from reaction of **4** with chloroformate.

Interestingly when these same four conditions were applied to the substituted oxetanol system **10** (R_1 = Me, R_2 = H) no reaction was observed. This lack of reactivity persisted even in the case of LiCl which was heated to reflux. These observations are in stark contrast to the successful rearrangement of substituted oxetanols under acid catalysis (entries 8−12). It is likely that in these nonacid-catalyzed cases, where the oxygen atom in the oxetane ring is unprotonated, nucleophilic attack on the now secondary oxetane center is severely restricted. The failure of these oxetane-substituted examples to undergo reaction indicates that an S_N2 mechanism operates under these nonacidic conditions. If an S_N1 mode was operating, then it would be expected that ring-opening would be facilitated with increasing substitution. As mentioned earlier, however, the fact that minor amounts of a diastereomer resulting from inversion are observed (entries 8−12) cannot rule out a mixed S_N2/ S_N1 pathway under acid conditions.

Scheme 3. Ring-Opening of Oxetanes under Nonacidic Conditions



In summary a novel acid-catalyzed rearrangement sequence of oxetane-fused azepines has been described. The

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reaction involves acid-catalyzed ring-opening of the oxetane ring followed by a series of transannular ring-opening and -closing reactions. In concert with the [5 + 2]/Norrish II reaction that precedes it this overall sequence provides a powerful two-step technique for the conversion of readily available maleimides into complex lactone-fused azatricycles.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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