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Tungsten Complex Induced Dehydration of 2,3-Dihydroxycarboxylic Acids to α-Keto Acids

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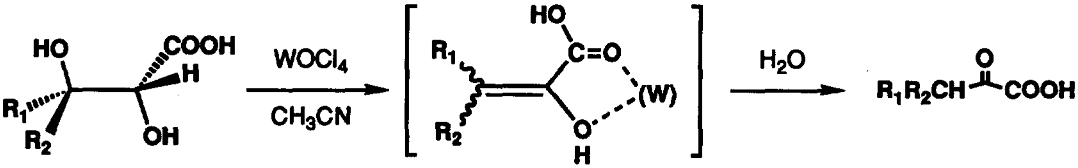
Abstract: In the absence of added base, $WOCl_4$ induces rapid dehydration of the title compounds to give α-keto acids. A mechanism is suggested based on a neighboring group effect.

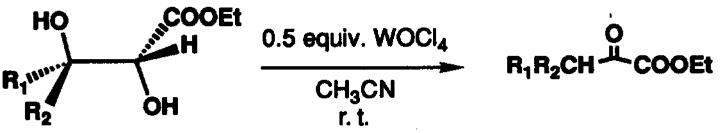
We have found a remarkable effect of base on the reaction between $WOCl_4$ and 2,3-dihydroxycarboxylic acids: as we previously noted,[1] dehydrative decarboxylation[2] of these substrates can be effected in high yield using W(VI) catalysis in the presence of TMEDA, either in relatively non-polar chlorobenzene or in polar acetonitrile; when base is omitted, the reaction pathway changes entirely to high yield, simple dehydration to the α-keto acid. In a typical procedure, a mixture of 0.015 g (0.10 mmol) of either *erythro*-[3] or *threo*-2,3-dihydroxyhexanoic acid[4], 0.034 g (0.10 mmol) of $WOCl_4$ and 0.70 mL of CD_3CN was prepared in an NMR tube under nitrogen, cooled by liq. N_2, evacuated, and sealed. Under these conditions, it was possible to observe (^{1}H NMR) chelate complexes of the acids and W-enol complex **1**, the primary dehydration product of the acid,[5] both of which formed rapidly at room temperature and which slowly hydrolyzed to the α-keto acid.

Scheme 1.



1

Overall dehydration also occurs for esters. For example, ethyl *threo*-2,3-dihydroxybutanoate (80 mg; 0.54 mmol) was treated with $WOCl_4$ (92 mg; 0.27 mmol) in 11 ml of acetonitrile at room temperature; hydrolysis, filtration and analysis yielded ethyl 2-oxobutanoate (64 mg; 0.49 mmol; 91%). Under these conditions, neither the simple 3-hydroxycarboxylic acid nor its esters dehydrate.

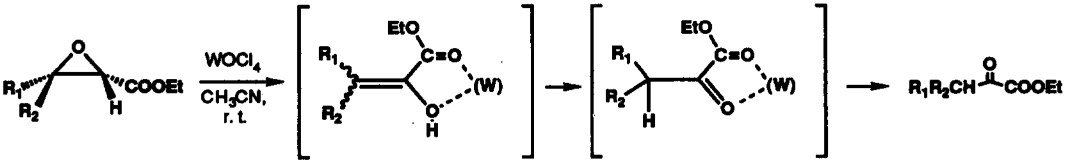


Ester	Time (days)	Product	Yield (%)[a]
$R_1 = CH_3$; $R_2 = H$	1	$CH_3CH_2COCO_2Et$	91
$R_1 =$ *n*-Pr; $R_2 = H$	1	$CH_3(CH_2)_2COCO_2Et$	78
$R_1 = H$; $R_2 =$ *n*-Pr	1	$CH_3(CH_2)_2COCO_2Et$	81
$R_1 =$ *i*-Pr; $R_2 = H$	3	$(CH_3)_2CHCH_2COCO_2Et$	84
$R_1 = CH_3$; $R_2 = CH_3$	3	$(CH_3)_2CHCOCO_2Et$	81

[a] by gc

Dehydration does not occur by general acid catalysis: *threo*-2,3-dihydroxyhexanoic acid was stable in CD_3CN to added aqueous HCl. $WOCl_4$ could activate an hydroxyl as a leaving group by direct coordination, or it could acidify an α-proton by carboxyl group coordination, or do both, by chelation. *Erythro*- and *threo*-2,3-dihydroxyhexanoic acids gave the same dehydration product **1**;[5] this suggests either that the dehydration step is not stereospecific or that **1** *E/Z* isomerizes. Dehydration of the 2,3-dihydroxy acid may occur through an epoxy acid intermediate followed by α-C-H bond deprotonation: When ethyl *trans*-2,3-epoxybutanoate **2** ($R_1 = H$, $R_2 = CH_3$) was treated with 1 equiv. of $WOCl_4$ in dry CD_3CN after 30 min at room temperature, both the enol ester of **1**[6] and tungsten-coordinated α-keto ester, **3**,[7] were formed (Scheme 2). Starting material was totally consumed after 4 hrs. When 1 equiv. of water was added to a mixture of ethyl *trans*-2,3-epoxybutanoate and 1 equiv. of $WOCl_4$ in CD_3CN, a third compound was also formed,[8] assigned as a complex of ethyl *erythro*-2,3-dihydroxybutanoate formed by *anti* attack on the oxirane unit. Thus the epoxy ester and the ethyl 2,3-dihydroxycarboxylate may be in equilibrium in the presence of W catalysis. This complex slowly dehydrated to give W-coordinated α-keto ester and then the free product.

Scheme 2.

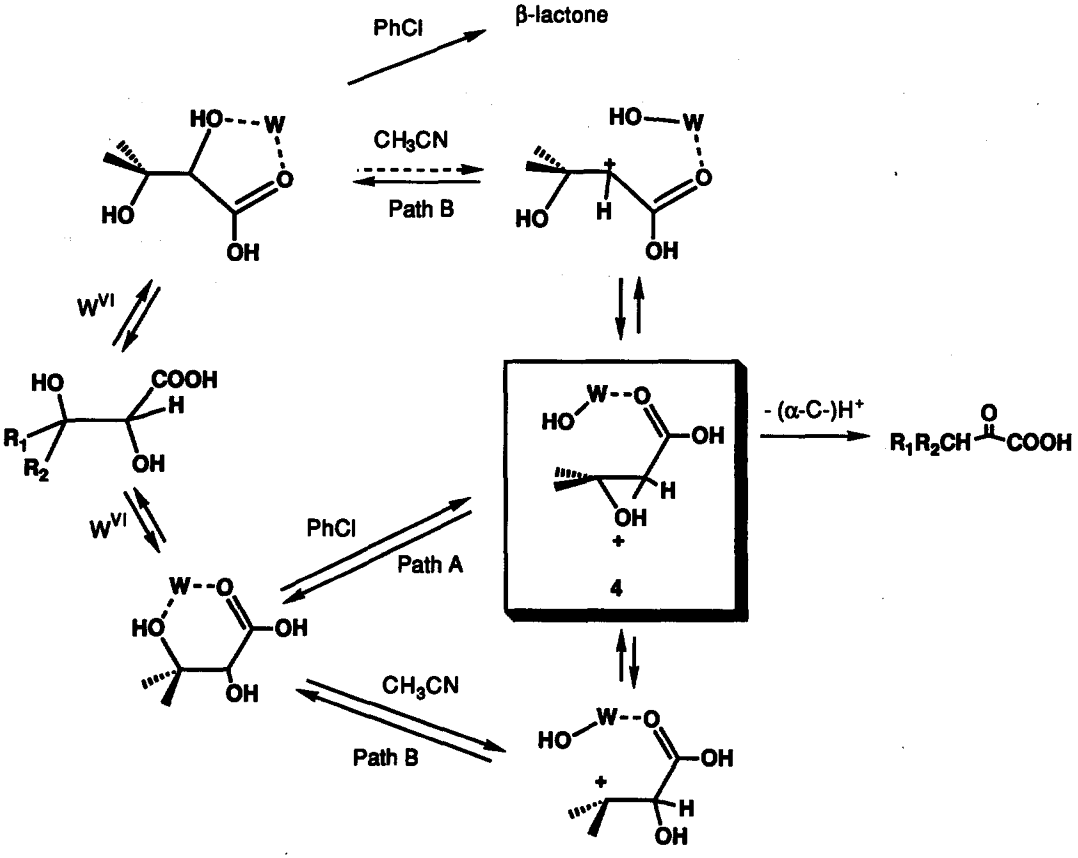


2 1 (ester) 3

Two competing metal-assisted paths to the ketoacid may be envisaged, one involving the [3-OH,CO_2H] chelate[1] and the other the [2-OH,CO_2H] isomer. In either case, coordination of OH to W could activate that substituent as a leaving group; however, heterolytic -OH loss from [2-OH,CO_2H] seems less likely because of the α-relationship of that -OH and the W-coordinated carboxylic carbonyl group (Scheme 3). In chlorobenzene for the cases studied, keto acids were formed readily >150°, and *erythro* and *threo* disasteromers were comparably reactive, ratewise. Qualitative rates for dehydration correlated inversely with the size of the substituent at C3, suggesting S_N2 attack at that carbon by 2-OH (path A). In contrast, in acetonitrile, substitution at C3 did not slow dehydration, suggesting an S_N1 type process (path B) in that more polar solvent.

The ratio of TMEDA to $WOCl_4$ employed is critical to the success of either simple dehydration or dehydrative decarboxylation.[1] We note that at low $WOCl_4$: TMEDA, simple dehydration dominates, but at 1:3, this process is suppressed in either chlorobenzene or acetonitrile. In the reaction between 3-hydroxycarboxylic acids and $WOCl_4$, amines do not coordinate to tungsten but act only as Brønsted bases.[2] Perhaps a high relative ratio of TMEDA to W suppresses simple dehydration by deprotonation of the epoxy intermediate 4 at oxygen, making subsequent α-C-H bond deprotonation unfavorable.

Scheme 3.



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References and Notes

1. Bae Yu, H. K.; Schwartz, J. see the accompanying manuscript.

2. Tanzawa, T.; Schwartz, J. *Organometallics* **1990**, *9*, 3026.

3. Armstrong, F. B.; Lipscomb, E. E.; Crout, D. H. G.; Morgan, P. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 691.

4. *threo*-2,3-Dihydroxyhexanoic acid was prepared from *trans*-2-hexenoic acid by osmolysis.

5. Both complexes **1** may be identical: from *threo*-2,3-dihydroxyhexanoic acid, ^{1}H NMR (solvent) δ6.49 (t, J = 8.4 Hz), 2.72 (q); from *erythro*-2,3-dihydroxyhexanoic acid, δ6.50 (t, J = 8.1 Hz), 2.72 (q); similarly from *threo*-2,3-dihydroxybutanoic acid, δ6.51 (q, J = 7.6 Hz), 2.39 (d); from *erythro*-2,3-dihydroxybutanoic acid, δ6.54 (q, J = 7.6 Hz), 2.39 (d).

6. Chemical shift data for **1-ester** (δ5.16 [q, J = 6.6 Hz], 1.61 [d, J = 6.6 Hz]) were somewhat different from those of **1** and may be due to changes in preferred coordination geometries for the two types of carboxyl groups.

7. δ3.41 (q, J = 6.9 Hz), 1.11 (t, J = 6.9 Hz); *cf.* for free ethyl 2-oxobutanote: δ2.83 (q, J = 7.3 Hz), 1.03 (t, J = 7.3 Hz).

8. δ5.70 (d, J = 10.5 Hz), 4.86 (dq, J = 6.9, 10.5 Hz), 1.33 (d, J = 6.9 Hz).

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