Behaviour of Dioxolanones as Chiral Acyl Anion Equivalents

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Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Abstract: The 1,3-dioxolan-4-ones readily derived from α-hydroxy acids act as convenient acyl anion equivalents by deprotonation – alkylation followed by flash vacuum pyrolysis. Conjugate addition of their anions to ethyl crotonate similarly gives β-methyl-γ-oxo esters and by using chiral dioxolanones these can be obtained in up to 86% e.e.

We recently reported that ethyl mandelate acts as a convenient benzoyl anion equivalent for the formation of alkyl aryl ketones by deprotonation – alkylation followed by flash vacuum pyrolysis.[1] This procedure was not ideal however, requiring two equivalents of strong base, proceeding poorly for certain electrophiles such as benzyl and allyl halides, and not being applicable to aliphatic α-hydroxy esters. We have now been able to overcome all these drawbacks by using 1,3-dioxolan-4-ones and furthermore we have extended the method to provide chiral acyl anion equivalents.

The dioxolanones **1** and **2** were readily prepared by acid catalysed condensation of mandelic acid with acetone and lactic acid with dimethoxypropane, respectively. Alkylation of **1** with LDA and a variety of electrophiles provided the products **3** in moderate to good yield (Table 1). The outcome of the pyrolysis of **3** was by no means certain since a previous study of dioxolanone pyrolysis established that, depending on the substituents present, there may be either loss of CO to give two carbonyl compounds or loss of CO_2 to give an epoxide.[2] In the event, flash vacuum pyrolysis (FVP) of **3a-c** at 600 °C and 10^{-2} Torr resulted in clean loss of acetone and CO to give the ketones **4** (Table 1). For **3a** this was accompanied by some double bond isomerisation to give the conjugated enone. Hydrogenolysis of **3c** afforded **3d** in excellent yield and the successful pyrolysis of the latter to give α-hydroxyacetophenone **4d** seemed to bode well for the pyrolysis of **3e,f** derived from reaction of **1** with benzaldehyde and crotonaldehyde, respectively. Unfortunately however, the loss of acetone and CO in these cases was accompanied by a thermal retro-acyloin reaction to give two molecules of benzaldehyde from **3e** and benzaldehyde and crotonaldehyde from **3f**. As a prelude to our later studies in the chiral series, **2** was found to undergo 1,4-addition to ethyl crotonate to give **5** which upon FVP at 550 °C afforded the γ-oxo ester **6** in excellent yield.

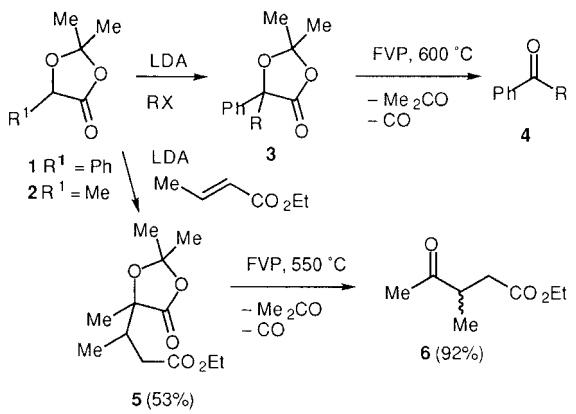


Table 1

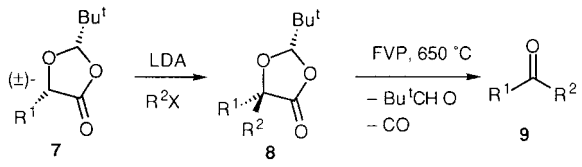
	R	Yield of **3** (%)	Yield of **4**(%)
a	H_2C=$CHCH_2$	94	26[a]
b	$PhCH_2$	86	97
c	$PhCH_2OCH_2$	51	63
d	$HOCH_2$	92[b]	75
e	PhCH(OH)	86	—
f	MeCH=CHCH(OH)	30	—

[a] The isomer PhCOCH=CHMe (27%) was also formed
[b] From hydrogenolysis of **3c**

Although both mandelic and lactic acid are readily available in enantiomerically pure form, deprotonation at the α-carbon results in loss of the stereochemical information. However this problem was elegantly solved some years ago by Seebach and coworkers using the pivalaldehyde-derived dioxolanones **7** and the principle of self regeneration of stereogenic centres.[3] It occurred to us that, so long as the pyrolysis of the 2-t-butyldioxolanones followed the same route as the 2,2-dimethyl compounds above, this might provide a new type of chiral acyl anion equivalent.[4] Using the racemic acids we first prepared the *cis*-dioxolanones **7** using the reported procedure and checked that the reactions would take the desired course with simple alkyl halides as the electrophile. As shown in Table 2, **8a,b** were formed in satisfactory yield, and FVP at 650 °C afforded butyrophenone **9a** and phenylacetone **9b**, respectively. For a chiral acyl anion equivalent to be of any value, it must be reacted with an electrophile in which a new stereogenic centre is formed. The reaction of **7** with benzaldehyde and crotonaldehyde to give **8c,d** was therefore carried out. Unfortunately, as before for **3e,f**, FVP was accompanied by a retro-acyloin reaction. Attempts to prevent this by alkylation of the hydroxy group before pyrolysis are currently in progress.

Table 2

	R^1	R^2	Yield of **8** (%)	Yield of **9** (%)
a	Ph	Pr	95	60
b	Me	$PhCH_2$	58	56
c	Ph	PhCH(OH)	33	—
d	Ph	MeCH=CHCH(OH)	63	—



Despite a great deal of work on these systems, 1,4-addition to α,β-unsaturated carbonyl compounds has been little examined. As mentioned above, reaction of the anions of either **1** or **7** with crotonaldehyde results in almost exclusive 1,2-addition. The main other

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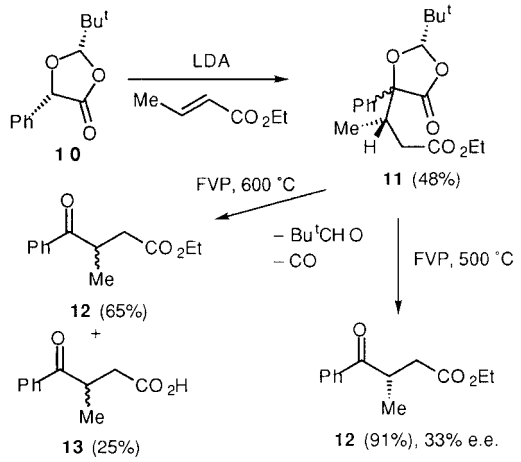
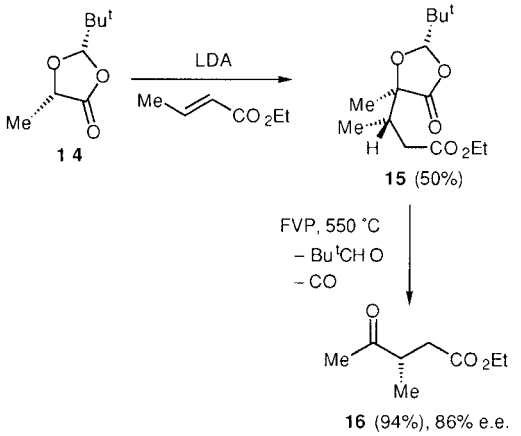
conjugate addition studied in detail by Seebach and coworkers is to nitroalkenes.[5] Following the successful formation and pyrolysis of **5** to give **6**, the enantiomerically and diastereomerically pure dioxolanone **10** was prepared from (*S*)-mandelic acid and pivalaldehyde using the literature method.[6] This was added to LDA at –78 °C and then allowed to warm to –20 °C before recooling to –78 °C and adding ethyl crotonate to give **11** as a 4:3 mixture of two major diastereomers. This was initially subjected to FVP at 600 °C which did result in loss of pivalaldehyde and CO to give the desired product **12** in 65% yield, but this was accompanied by the acid **13** formed by loss of ethene and, more seriously, both products were formed with low e.e. Conversion of **13** to its methyl ester with CH_2N_2 and comparison with the literature optical rotation[7] indicated an e.e. of 4% in favour of the (*S*)-enantiomer. A dramatic improvement was obtained by lowering the furnace temperature to 500 °C which gave **12** as the sole product in 91% yield and determination of the enantiomeric purity of this by ^{1}H NMR using the chiral lanthanide shift reagent (CLSR) Eu(hfc)$_3$ gave a value of 33% e.e. We interpret these results in terms of **11** being formed with essentially complete selectivity for the (*S*) stereochemistry at the CHMe centre but as a 4:3 mixture of epimers at C-5 of the ring. The conditions required for the pyrolysis result in partial racemisation of the product.





When the dioxolanone **14** formed from (*S*)-lactic acid was deprotonated using the same procedure and ethyl crotonate added, the corresponding product **15** was formed, this time essentially as a single diastereomer. Upon FVP at 550 °C this gave an excellent yield of ethyl 3-methyllaevulinate **16**.[8] In contrast to **12**, this compound has been prepared before in enantiomerically pure form by an enzymatic method.[9] Comparison of the sign and magnitude of the optical rotation indicated an e.e. of 86% in favour of the (*S*)-(–)-enantiomer which was in agreement with the value obtained by the CLSR method.

We have thus shown that the dioxolanones can behave as among the most straightforward and effective chiral acyl anion equivalents reported so far. Work is currently in progress to improve the yield of the conjugate addition reactions (the balance of material in the formation of **5**, **11** and **15** is accounted for by recovered starting materials), to overcome the problem of the retro-acyloin reaction for 1,2-adducts to carbonyl electrophiles, and to extend the range of α-hydroxy acids and electrophiles which can be used.

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References and Notes

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(8) **Typical Experimental Procedures**

Preparation of **5** A solution of **2**[10] (4.0 g, 30.8 mmol) in dry THF (4 cm^3) was added to a solution of LDA (33.8 mmol) in dry THF (25 cm^3) at –78 °C under nitrogen. After 30 min a solution of ethyl crotonate (3.87 g, 33.8 mmol) in dry THF (4 cm^3) was then added and the mixture stirred at –78 °C for 2 h and at RT for 2 h before adding to saturated aqueous NH_4Cl. Extraction with ether, drying and evaporation followed by Kugelrohr distillation afforded **5** (4.0 g, 53%) as a colourless liquid, bp (oven temp.) 150 °C at 0.005 Torr (M^+, 244.1317. $C_{10}H_{20}O_5$ requires *M*, 244.1311); υ_{max} / cm^{-1} 1775; δ_H 4.16 (2 H, q, *J* 7, C*H*$_2$Me), 2.72 (1 H, half AB pattern of d, *J* 14, 3, C*H*$_2$CH), 2.38 (1 H, m, CH$_2$C*H*), 2.13 (1 H, half AB pattern of d, *J* 14, 10, C*H*$_2$CH), 1.60 (6 H, s, 2 x Me), 1.48 (3 H, s, Me), 1.29 (3 H, t, *J* 7, CH$_2$*Me*) and 1.03 (3 H, d, *J* 7, CH*Me*); δ_C 174.9 (C=O), 172.7 (C=O), 109.8 (4ry), 82.1 (4ry), 60.8 (OCH$_2$), 37.6 (Me), 36.2 (CH$_2$), 29.1 (Me), 28.0 (Me), 22.7 (CH), 15.4 (Me) and 14.6 (Me); *m/z* (EI) 244 (M^+, 5%), 159 (8), 130 (26) 113 (80) 59 (50) and 43 (100).

Preparation of **15** A solution of **14**[5] (1.0 g, 6.3 mmol) in dry THF (3 cm^3) was added to a solution of LDA (6.9 mmol) in dry THF (10 cm^3) at –78 °C under nitrogen. After 30 min the mixture was allowed to warm to –20 °C for 30 min and then recooled to –78 °C. A solution of ethyl crotonate (0.79 g, 6.9 mmol) in dry THF (3 cm^3) was then added and the mixture stirred at –78 °C for 2 h and at RT for 2 h. Work up as above followed by flash column chromatography (SiO_2, hexane–ether, 7:3) gave **15** (0.86 g, 50%)

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as a colourless liquid, R_f 0.65 (mainly as one diastereomer) (Found: M+H$^+$, 273.1693. $C_{14}H_{25}O_5$ requires *M+H*, 273.1702); $[\alpha]^{25}_D$+6.1 (*c* 0.6 in THF); δ_H 5.20 (1 H, s, CH), 4.13 (2 H, q, *J* 7, C*H*$_2$Me), 2.68 (1 H, half AB pattern of d, *J* 15, 4, C*H*$_2$CH), 2.6–2.4 (1 H, m, C*H*Me), 2.15 (1 H, half AB pattern of d, *J* 15, 10, C*H*$_2$CH), 1.38 (3 H, s, *J* 7, Me), 1.25 (3 H, t, *J* 7, CH$_2$*Me*), 1.07 (3 H, d, *J* 7, CH*Me*) and 0.96 (9 H, s, Me$_3$); δ_C 175.0 (C=O), 172.2 (C=O), 109.0 (CH), 81.5 (4ry), 60.7 (CH_2), 36.0 (CH_2), 35.4 (CH), 34.8 (4ry), 23.3 (Me$_3$), 20.0 (Me), 14.8 (Me) and 14.2 (Me); *m/z* (CI) 273 (M+H$^+$, 62%), 229 (10) and 187 (100).

Pyrolysis of **5** FVP of **5** (1.66 g) at 550 °C and 10^{-2} torr using the apparatus reported previously[11] gave a colourless liquid at the furnace exit which proved to be ethyl 3-methyllaevulinate **6** (0.99 g, 92%); δ_H and δ_C identical to literature data.[9]

Pyrolysis of **15** FVP of **15** (91 mg) at 550 °C and 10^{-2} torr using the apparatus reported previously[11] gave a colourless liquid at the furnace exit which proved to be *(S)*-ethyl 3-methyllaevulinate **16** (49 mg, 94%); δ_H and δ_C as for **6**; $[\alpha]^{20}_D$–40.5 corresponding to an e.e. of 86% [Lit.,[9] $[\alpha]^{20}_D$–47.2 (*c*, 1.1 in MeOH)]; ^{1}H NMR using Eu(hfc)$_3$ (MeCO signal) also gave an e.e. of 86%.

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