## Kurzmitteilungen / Short Communications

# Facile Diastereoselective Synthesis of 2,6-Dialkyl-5-methylene-1,3-dioxan-4-ones via α-Activated Vinyl Esters

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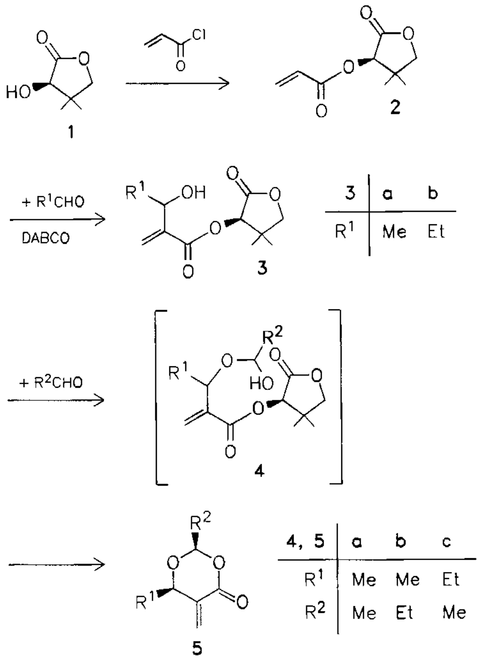
Vinyl esters such as **2**, in the presence of DABCO, undergo initial reaction with aldehydes, followed by nucleophilic attack on a second aldehyde molecule. Subsequent intramolecular transesterification affords the dioxanones **5** in high yields and high diastereomeric excesses.

In our endeavours to find new areas of application for the reaction of "potential vinyl carbanions" with aldehydes[1-3], we have developed a novel cyclization reaction. The vinyl ester **2**[4], activated by the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), reacts initially with acetaldehyde in the usual aldol manner. However, in this instance, a further reaction occurs with a second molecule of the aldehyde, followed by an intramolecular transesterification to afford the substituted 1,3-dioxanone **5a** (Scheme 1). This product is obtained in 87% chemical yield and has a diastereomeric excess of 84% $\langle[\alpha]^{22}_{D} = -5.6$ ($CHCl_3$, 2.1)$\rangle$.

Scheme 1

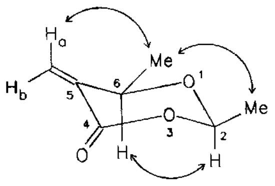


| | 5a | 5b | 5c |
|---|---|---|---|
| yield (%) | 87 | 86 | 83 |
| d.e. (%) | 84 | 88 | 86 |

This novel reaction is versatile in that various alkyl substituents may be introduced to the 2- and 6-positions of the dioxanone. In addition, it is very much faster than the classical reaction reported by Baylis and Hillman[5,6] (30 min as opposed to 7 d), and the alcohol released on cyclization is recovered as the optically pure compound. However, while high diastereomeric excesses are obtained, only low enantiomeric excesses have been obtained to date.

A critical factor in this cyclization reaction is the choice of acrylate ester. With the usual alkyl esters, e.g. methyl and ethyl, no cyclization occurs, and the reactions can take up to 7 d for completion[5]. However, with the pantolactone ester **2**, the reaction is complete within 30 min. With acrylate esters such as the lactate and mandelate, which also incorporate the α-hydroxy carbonyl system, the reaction times are also fast (24 h), but slower than for the pantolactone ester. This reaction thus provides easy entry into a series of highly functionalised 1,3-dioxan-4-ones by a route not previously explored.

In order to determine the stereochemistry of **5a** it was examined at 500 MHz for nuclear Overhauser effects. These studies showed unambiguously that **5a** adopts the conformation shown in Figure 1. Those atoms or groups showing strong enhancement are indicated by the arrows. The two methyl groups are *cis* relative to one another. Comparison of the $^1$H- and $^{13}$C-NMR shift values for the two methyl substituents with closely related compounds prepared by Anteunis et al.[7] and Pihlaja et al.[8] confirm the above assignment.



5a

Figure 1. Conformation of **5a** according to NOE

Although **5a** was obtained in high diastereomeric excess, the enantiomeric excess [determined with $Eu(fod)_3$ as a chiral shift reagent] was only 10%. Compound **5a** thus consists of a mixture of

15 parts of the (*RR*)/(*SS*) enantiomeric pair and 1 part of the (*SR*)/(*RS*) enantiomeric pair.

The generality of this novel cyclization with a variety of aliphatic aldehydes (added consecutively) was demonstrated with the preparation of the substituted dioxanones **5b,c** ($R^1 \neq R^2$; >80% yield, >80% d.e., 10% e.e.) shown in Scheme 1.

Procedures are now being investigated to improve the enantioselectivity of this reaction. Enantiomerically pure compounds such as **5** possess considerable potential as synthetic intermediates on account of the multiplicity of functional groups and their ease of formation. Recently, Seebach and co-workers[9,10] have prepared substituted 1,3-dioxan-4-ones with high e.e.'s using very different procedures. These compounds, although less functionalised than those in our series have proved to possess considerable synthetic potential.

## Experimental

$^1$H NMR and $^{13}$C NMR: Varian FT-80A (80 MHz), using TMS/$CDCl_3$ as internal standards. – NOE experiments: Bruker WM-500 (500 MHz). – Elemental analyses: Perkin-Elmer 240B Elemental Analyser. – GC/MS: Hewlett-Packard 5890 gas chromatograph and 5988A spectrometer. – Specific rotations: Atago Polax-D Digital Polarimeter.

*2,6-Dimethyl-5-methylene-1,3-dioxan-4-one* (**5a**): Ethanal (2.5 equiv.) is added to a suspension of the vinyl ester **2** (1.0 equiv.) and DABCO (20 mol-% of the ester **2**) and the solution stirred in a stoppered flask at 20–30°C for 30 min. The reaction mixture is quenched and **5a** isolated by flash chromatography (diethyl ether/hexane) in 87% yield. – $^1$H NMR: $\delta$ = 1.48 (d, 3H, 6-$CH_3$), 1.51 (d, 3H, 2-$CH_3$), 4.66 (m, 1H, 6-H), 5.51 (q, 1H, 2-H), 5.61 and 6.51 (2 dd, 2H, 5-$CH_2$). – $^{13}$C NMR ($CDCl_3$, 80 MHz): $\delta$ = 19.95 (t), 20.55 (t), 73.69 (d), 99.18 (d), 125.17 (t), 137.56 (s), 162.87 (s). – MS (70 eV): *m/z* (%) = 142 (0.6) [$M^+$], 127 (18), 98 (12), 83 (51), 54 (100), 43 (20). – $[\alpha]_D^{22} = -5.6$ ($CHCl_3$, $c$ = 2.1)

$C_7H_{10}O_3$ (142.2) Calcd. C 59.15 H 7.09
Found C 59.24 H 7.04

*2-Ethyl-6-methyl-5-methylene-1,3-dioxan-4-one* (**5b**): Ethanal (1.0 equiv.) is added to a suspension of the vinyl ester **2** (1.0 equiv.) and DABCO (20 mol-% of the ester **2**) and the solution stirred in a stoppered flask at 20–30°C for 20 min. Propanal (1.0 equiv.) is then added and the reaction mixture stirred for a further 30 min. The reaction mixture is quenched and **5b** isolated by flash chromatography (diethyl ether/hexane) in 79% yield. – $^1$H NMR: $\delta$ = 0.99 (t, 3H, $CH_2C\mathit{H}_3$), 1.45 (d, 3H, 6-$CH_3$), 1.70 (m, 2H, $C\mathit{H}_2CH_3$), 4.57 (m, 1H, 6-H), 5.31 (t, 1H, 2-H), 5.63 and 6.40 (2 dd, 2H, 5-$CH_2$).

$C_8H_{12}O_3$ (156.2) Calcd. C 61.52 H 7.75
Found C 61.43 H 7.79

*6-Ethyl-2-methyl-5-methylene-1,3-dioxan-4-one* (**5c**): Propanal (1.0 equiv.) is added to a suspension of the vinyl ester **2** (1.0 equiv.) and DABCO (20 mol-% of the ester **2**) and the solution stirred in a stoppered flask at 20–30°C for 30 min. Ethanal (1.0 equiv.) is then added and the reaction mixture stirred for a further 30 min. The reaction mixture is quenched and **5c** isolated by flash chromatography (diethyl ether/hexane) in 76% yield. – $^1$H NMR: $\delta$ = 0.98 (t, 3H, $CH_2C\mathit{H}_3$), 1.50 (d, 3H, 2-$CH_3$), 1.66 (m, 2H, $C\mathit{H}_2CH_3$), 4.54 (m, 1H, 6-H), 5.50 (q, 1H, 2-H), 5.63 and 6.45 (2 dd, 2H, 5-$CH_2$).

$C_8H_{12}O_3$ (156.2) Calcd. C 61.52 H 7.75
Found C 61.56 H 7.76

CAS Registry Numbers

**2**: 84822-49-1 / **5a**: 126134-25-6 / **5b**: 126134-23-4 / **5c**: 126134-24-5 / ethanal: 75-07-0 / propanal: 123-38-6

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[26/90]