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LETTERS

Titanium tetrachloride promoted reaction of silyl ketene acetals with epoxides: a new method for the synthesis of γ-butanolides

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Abstract—A new method for the synthesis of γ-butanolides is described. The titanium tetrachloride promoted reaction of silyl ketene acetals with epoxides, followed by acidic work-up, affords the corresponding butyrolactones in 44–83% yield. © 2002 Elsevier Science Ltd. All rights reserved.

Contrary to nucleophilic epoxide ring opening with organometallic reagents, which constitutes a well established and synthetically highly useful method of carbon–carbon bond formation,[1] examples of epoxide reactions with enolates are scarce.[2] Lithium enolates of ketones and esters are unreactive towards epoxides, which generally precludes the application of what would probably be the most efficient approach to homoaldols and butyrolactones (Fig. 1). Dianions of simple carboxylic acids react with epoxides,[3] however, a large excess of dianion and forcing conditions are often required. Transmetallation of lithium ester enolates with diethylaluminium chloride affords the more reactive aluminium enolates, whose reactions with epoxides afford the γ-hydroxy esters in moderate to good yields.[4] In order to circumvent the aforementioned problems, indirect methods have been devised, based on the application of diethylethoxyalkynylalane,[4a] or silylynamine,[5] as the acetate enolate equivalents; these approaches are limited to the synthesis of α-unsubstituted butanolides, although the latter offers some possibilities to achieve molecular diversity.

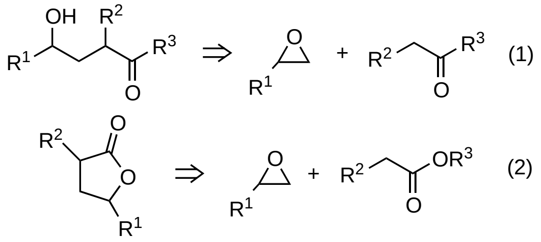
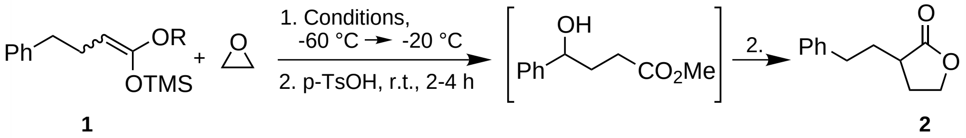


Figure 1.

Recently, we have shown that enoxysilanes react with epoxides in the presence of $TiCl_4$ to give homoaldol products in moderate to good yields, thus enabling the



1 **2**

Conditions: R = ^{i}Pr, solvent = CH_2Cl_2 19%
R = Me, solvent = CH_2Cl_2 38%
R = Me, solvent = *n*-hexane : CH_2Cl_2 = 2 : 1 62%

Scheme 1.

Keywords: epoxides; ketene acetals; lactones; titanium and compounds; alkylation.

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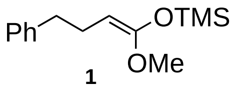
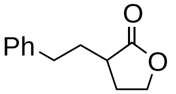
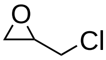
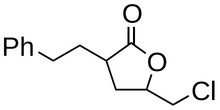
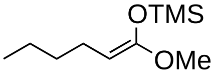
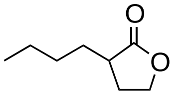
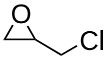
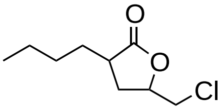
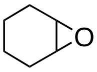
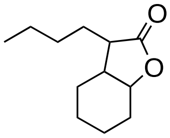
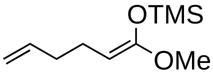
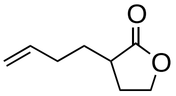
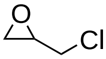
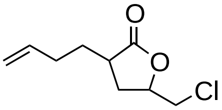
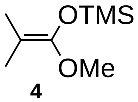
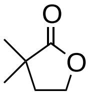
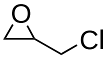
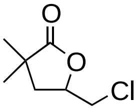
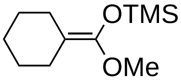
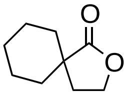
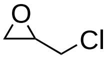
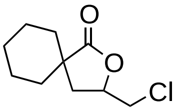
Table 1. $TiCl_4$ promoted reactions of silyl ketene acetals with epoxides[a]

Entry	Silyl ketene acetal	Epoxide	Product	Yield [b]
1	 **1**		 **2**	62% (97%) [c]
2				49%[d]
3				69%
4				64%[d]
5			 **3**	48%[d]
6				64%
7				83%[d]
8	 **4**			53%
9				44%
10	 **5**		 **6**	66%
11				69%

a) For the experimental procedure, see ref. 8; b) Yields of isolated, pure compounds; c) Calculated on the basis of the converted starting compound; d) Obtained as a 1:1 mixture of diastereoisomers.

transform shown in Eq. (1) (Fig. 1).[6] Herein, we report the extension of this new reaction to silyl ketene acetals, whose reactions with epoxides under modified Mukaiyama conditions afford γ-butanolides (the overall transformation corresponding retrosynthetically to Eq. (2), Fig. 1).

When a dichloromethane solution of ethylene oxide and silyl ketene acetal **1**,[7] derived from isopropyl 4-phenylbutanoate, was treated with $TiCl_4$ at −60→−20°C, TLC of the reaction mixture indicated the formation of two compounds which, upon treatment with a catalytic amount of *p*-TsOH during work-up, converged to a single product, identified as α-(2-phenylethyl)-γ-butanolide **2** (19%, Scheme 1). Other Lewis acids ($BF_3·Et_2O$, $ZnCl_2$, $Ti(O^iPr)_4$, $SnCl_4$) proved inferior catalysts with respect to $TiCl_4$. Substituting the smaller methyl group for isopropyl in **1** resulted in a yield enhancement to 38%. After some experimentation it was found that the reaction is best carried out in a mixed solvent: *n*-hexane/dichloromethane = 2/1; under these conditions lactone

2 was isolated in 62% yield, along with some unreacted methyl 4-phenylbutanoate (97% yield, based on the recovered starting material).

The generality of the procedure was tested by reacting several structurally different silyl ketene acetals with ethylene oxide under the described conditions.[8] In all cases the corresponding lactones were obtained in good yields (Table 1, entries 1, 3, 6, 8 and 10). Formation of α,α-disubstituted butanolides from α,α-disubstituted silyl ketene acetals indicates the ease of formation of quaternary centres (entries 8 and 10). The reaction with cyclohexanecarboxylic ester derived silyl ketene acetal **5** produced a spirobicyclic lactone **6** (entry 10). In addition to ethylene oxide, reactions with epichlorohydrin were also studied: in all cases 4-chloromethyl substituted butanolides were obtained in good yields, resulting from a nucleophilic attack at the less substituted epoxide carbon (entries 2, 4, 7, 9, and 11).[9] Cyclohexene oxide, a 1,2-disubstituted epoxide, gave rise to a condensed bicyclic lactone **3** (entry 5). Reactions of **1**, **4** and **5** with propene oxide afforded mixtures of regioisomeric lactones in modest yields (30–40%).

To summarize, a new method for effecting ester/epoxide coupling under non-basic conditions is described, which may prove a useful complement to existing methodology for γ-butanolide formation.

Acknowledgements

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8. Typical experimental procedure: *2-(2-Phenylethyl)-4-butanolide* **2**. To a cold (−60°C) solution of **1** (250 mg; 1 mmol) and ethylene oxide (88 mg; 100 μL; 2 mmol) in *n*-hexane:CH$_2$Cl$_2$ = 2:1 (3 mL), a solution of TiCl$_4$ in CH$_2$Cl$_2$ (0.88 mL of 3.65 M; 3 mmol) was added dropwise, with stirring under an argon atmosphere. After the addition was complete, the reaction mixture was allowed to reach −20°C, then cooled to −30°C and quenched with a saturated aqueous solution of NH$_4$Cl (5 mL). The reaction mixture was partitioned between water and CH$_2$Cl$_2$, a catalytic amount of *p*-TsOH was added to the organic solution and the mixture was stirred for 3 h at ambient temperature. Usual work-up, followed by purification by dry-flash chromatography (SiO$_2$; eluent: 20% acetone in petroleum-ether) afforded 117 mg (62%) of the title compound **2** as a colourless oil. E$_{0.3}$135–145°C (Kugelrohr); IR$_{\text{film}}$: 3063, 3029, 2922, 2861, 1769, 1495, 1454, 1376, 1184, 1150, 1026; ^{1}H NMR (200 MHz, CDCl$_3$): 7.40–7.10 (m, 5H); 4.34 (ddd, $J_1 = J_2 = 9.1$ Hz, $J_3 = 2.7$ Hz, 1H); 4.16 (ddd, $J_1 = J_2 = 9.1$ Hz, $J_3 = 6.6$ Hz, 1H); 2.85–2.60 (m, 2H); 2.60–2.10 (m, 3H); 2.10–1.60 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): 179.3; 140.7; 128.4; 128.3; 126.1; 66.3; 38.2; 33.1; 31.8; 28.6; MS (EI) *m*/*z*: 190 (M^+; 17%); 105 (15%); 91 (25%); 85 (100%); HRMS (EI): M^+, found 190.09967, C$_{12}$H$_{14}$O$_2$ requires 190.09938.
9. These products were obtained as 1:1 mixtures of diastereoisomers which could not be separated by column chromatography, but were separated by preparative gas chromatography. Spectral data for *2-(3-butenyl)-4-chloromethyl-4-butanolide* (entry 7): E$_{0.3}$100–105°C (Kugelrohr, for the mixture of isomers); Anal. Calcd for C$_9$H$_{13}$O$_2$: C, 57.30; H, 6.95; Found: C, 56.98; H, 6.98; Isomer **A**: IR$_{\text{film}}$: 3074, 2919, 2862, 1774, 1641, 1347, 1170, 1038; ^{1}H NMR (200 MHz, CDCl$_3$): 5.90–5.70 (m, 1H); 5.15–4.95 (m, 2H); 4.76 (app. hex., $J = 4.6$, 1H); 3.71 (dd, $J_1 = J_2 = 5.4$, 2H); 2.85–2.65 (m, 1H); 2.60–2.30 (m, 2H); 2.30–1.90 (m, 2H); 1.70–1.50 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): 178.6; 136.9; 115.9; 76.2; 46.0; 38.2; 31.2; 30.8; 30.3. Isomer **B**: 3074, 2939, 2864, 1775, 1641, 1345, 1172, 1037; ^{1}H NMR (200 MHz, CDCl$_3$): 5.89–5.69 (m, 1H); 5.15–4.95 (m, 2H); 4.60 (m, 1H); 3.71 (dd, $J_1 = 5.2$, $J_2 =$ 1.1, 2H); 2.80–2.40 (m, 2H); 2.30–2.00 (m, 3H); 1.95–1.50 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): 177.8; 137.0; 115.9; 76.3; 45.3; 39.6; 32.2; 31.2; 29.4.