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α-METHYLENATION OF LACTONES AND ESTERS
ZINC BROMIDE-CATALYSED PHENYLTHIOMETHYLATION OF *O*-SILYLATED ENOLATES[1]

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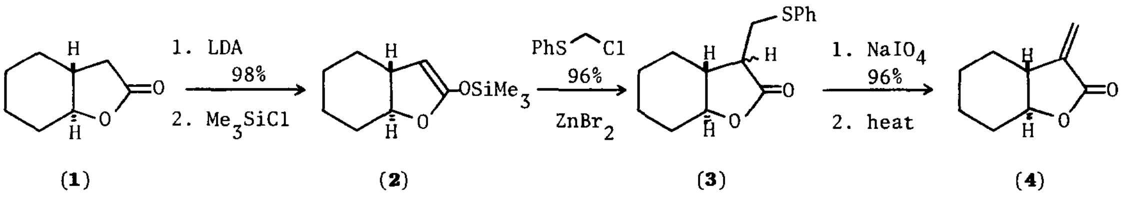
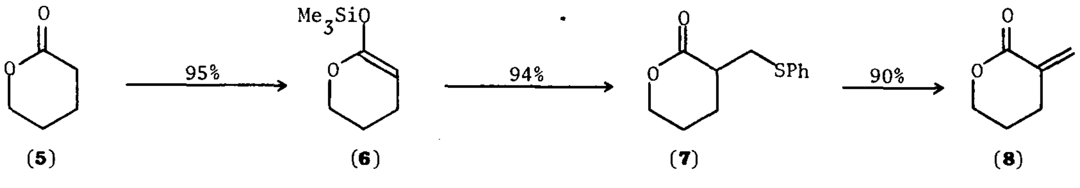
The α-methylene unit of α-methylene lactones[2] is a key feature of many cytotoxic sesquiterpenes; it can be protected by thioether formation by a Michael addition of thiols,[3,4] and subsequently regenerated under controlled conditions. Consequently, alkylation of a lactone enolate with an α-thioalkyl halide should lead directly to a masked α-methylenelactone. However, it has been found that lactone enolates are alkylated in only 0-20% yield by the alkyl halides, $PhSCH_2I$,[4] $MeSCH_2Cl$, $MeSCH_2I$,[2a,5] and $PhCH_2SCH_2Br$.[6]

We now report that lactone and ester enolates, when first *O*-silylated, can be phenylthiomethylated in high yield using chloromethyl phenyl sulphide[7] ($PhSCH_2Cl$) and mild Lewis acid catalysis with zinc bromide. This provides an efficient method for the α-methylenation of both lactones and esters: the overall yields for the sequences (**1**→**4**), (**5**→**8**), and (**9**→**11**) are 90%, 81%, and 87%, respectively.





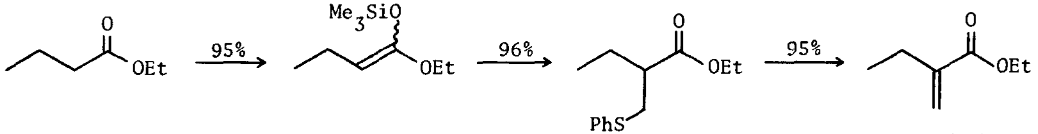
Treatment of the lithium enolate of the *trans*-fused γ-lactone (**1**), prepared by deprotonation of **1** with LDA in THF at -78°, with chlorotrimethylsilane gave, after non-aqueous isolation[8] and distillation, the *O*-silylated enolate (**2**). In the presence of a catalytic amount of powdered anhydrous zinc bromide (*ca.* 0.01 equivalents), the *O*-silylated derivative (**2**) reacted with $PhSCH_2Cl$ (1.2 equivalents) in dry dichloromethane. After 16 h at room temperature, the solvent was evaporated and the crude product chromatographed on silica gel to give the α-phenylthiomethyl-γ-lactone (**3**) as a mixture of diastereoisomers. Stronger Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3.OEt_2$ were ineffective in this reaction, while $ZnCl_2$ gave lower yields. The α-methylene unit was unmasked[4] by sodium metaperiodate oxidation of **3** in aqueous methanol followed by sulph-

oxide thermolysis in CCl_4-$CHCl_3$ (80°, 14 h) to give the methylene- -lactone ( ). Analogously

oxide thermolysis in CCl_4-$CHCl_3$ (80°, 14 h) to give the α-methylene-γ-lactone (**4**). Analogously, $ZnBr_2$-catalysed reaction of **2** with $MeSCH_2Cl$ gave the α-methylthiomethyl-γ-lactones (**3**, Me for Ph; 80%), which has been unmasked in 90% yield by an alternative sequence of sulphonium salt formation with MeI followed by β-elimination with mild base.[5]

Our procedure can be applied to α-methylenation of δ-lactones as well as γ-lactones. The lithium enolate of δ-valerolactone (**5**) was *O*-silylated to give **6**, and then phenylthiomethylated with $PhSCH_2Cl$, catalysed by $ZnBr_2$, to give the masked α-methylene-δ-lactone (**7**), which, after sulphur oxidation and thermolysis (80°, 4 h) gave **8**.

Ester enolates also cannot be alkylated directly with $PhCH_2SCH_2Br$ in useful yield;[6] however, *O*-silylation followed by $ZnBr_2$-catalysed phenylthiomethylation is successful. For example, reaction of the ketene ethylsilylacetal (**10**) with $PhSCH_2Cl$ in CH_2Cl_2 (20°, 36 h), in the presence of $ZnBr_2$, gave the α-phenylthiomethyl ester (**11**), which in turn gave the α-methylene ester (**12**).



(**9**) (**10**) (**11**) (**12**)

The mild conditions required for phenylthiomethylation of lactones and esters via their *O*-silylated enolates, the ability to store the α-methylene group,[6] and the efficiency of unmasking combine to make this a superior method for the α-methylenation of lactones[2] and esters. It appears to be generally true that many alkylations of ketones and esters can be improved by changing from the basic conditions of enolate chemistry to the acidic conditions of silyl enol ether chemistry.[9]

NOTES and REFERENCES

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