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Application of enolates of activated carboxylic acid derivatives in organic synthesis—novel syntheses of β-lactones

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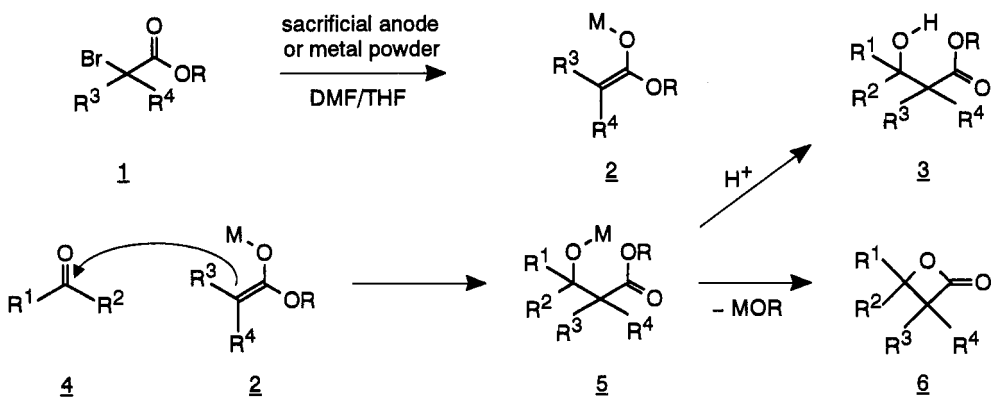
Abstract: Ester enolates derived from alkyl esters of alkanoic acids react with carbonyl compounds in an aldol type reaction forming alkyl β-hydroxyalkanoates. The substitution of an alkyl ester by the corresponding phenyl ester causes the formation of β-lactones *via* a spontaneous intramolecular cyclization of the intermediately formed *O*-metalated phenyl β-hydroxyalkanoates. This reaction is not restricted to enolates of activated esters. Enolates of other activated derivatives of carboxylic acids, such as benzotriazolides, are also useful starting materials for these versatile one-step β-lactone syntheses.

INTRODUCTION

Investigating the Reformatsky reaction of ethyl 2-bromo-2-methylpropanoate (1, R = Et, $R^3 = R^4$ = Me) with cyclohexanone [4, R^1–R^2 = $(CH_2)_5$] in DMF/THF at a sacrificial indium anode we obtained the α,α,β,β-tetrasubstituted β-lactone 6 in a yield of 80 % beside only 4 % of the expected β-hydroxy ester 3



Scheme 1. Synthesis of β-lactones 6 by Reformatsky reaction of ester enolates 2 with carbonyl compounds 4

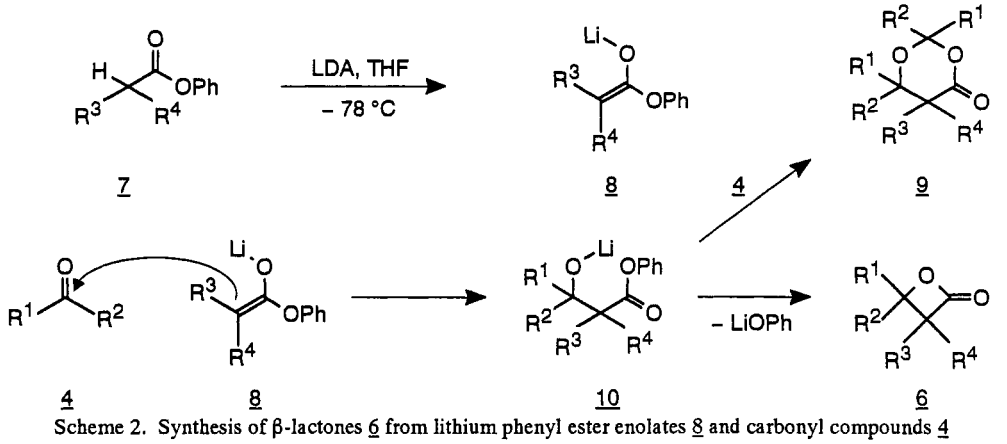
(Scheme 1). This surprising β-lactone synthesis is not due to the application of indium or the electrochemical procedure. Also under conventional Reformatsky conditions indium powder and even zinc powder afford in many cases the β-lactone 6 as the main product, providing the reaction is performed in DMF as sol-

vent. The reaction, however, is restricted to the formation of tetrasubstituted β-lactones. If aldehydes are used as carbonyl compounds and straight-chain alkyl α-bromoalkanoates for the generation of the indium or zinc enolates, only β-hydroxy esters are formed (ref. 1,2). Since less substituted β-lactones, especially α,β-disubstituted β-lactones, have been found as natural products with interesting pharmacological properties (ref. 3,4), we were interested in defining scope and limitations of this novel one-step β-lactone synthesis.

RESULTS

β-Lactones from carbonyl compounds and phenyl α-bromoalkanoates by the Reformatsky reaction. The unexpected spontaneous cyclization of the intermediately formed α,α,β,β-tetrasubstituted *O*-metalated alkyl β-hydroxyalkanoate 5 (M = $InBr_2$ or ZnBr) to the tetrasubstituted β-lactone 6 has been explained by the *gem*-dialkyl effect (ref. 5,6). In connection with attempts to broaden the scope of this synthesis to tri- and disubstituted β-lactones the question arose, whether the expected decrease of the *gem*-dialkyl effect could be compensated by a proper choice of the ester group, which has to be eliminated as metal alkoxide in the course of the β-lactone formation. Indeed, the application of phenyl α-bromoalkanoates 1 (R = Ph) instead of the corresponding alkyl esters allows the formation of α,β,β- and α,α,β-trisubstituted β-lactones 6 in 50–85 % yield by the electrochemical or conventional Reformatsky reaction of ketones with straight-chain phenyl α-bromoalkanoates and of aldehydes with α-branched phenyl α-bromoalkanoates, respectively. Unfortunately, the Reformatsky reaction of aldehydes with straight chain phenyl α-bromoalkanoates affords the corresponding α,β-disubstituted β-lactones 6 only in 10–25 % yield (ref. 7).

β-Lactones from carbonyl compounds and lithium ester enolates derived from phenyl alkanoates. Since the reactive intermediates 2 of the Reformatsky reaction are ester enolates, it was obvious to include lithium enolates 8 of phenyl alkanoates 7 into these investigations. Indeed, lithium enolates 8 prepared from phenyl

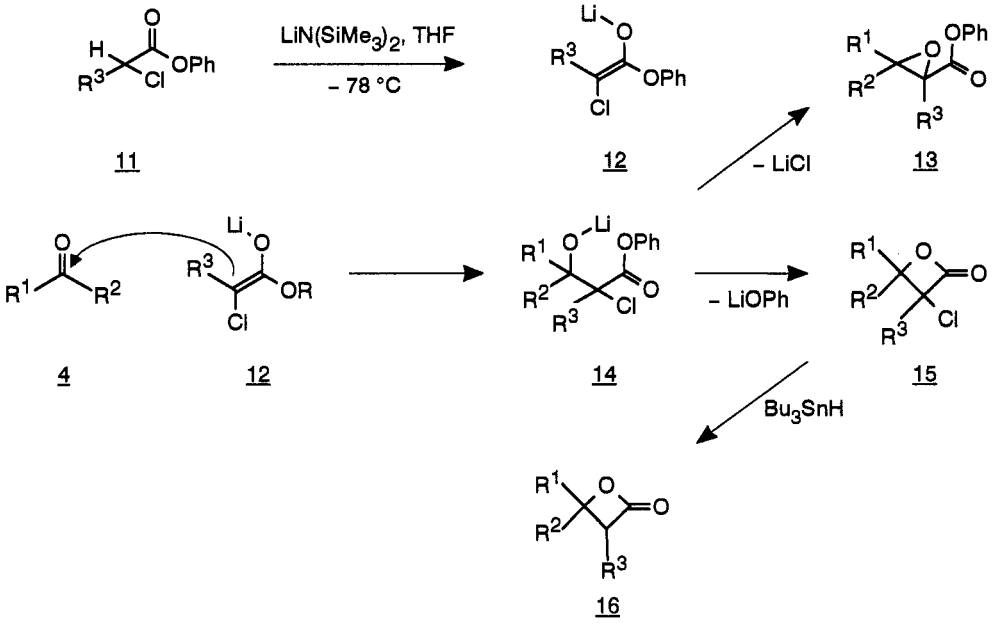


Scheme 2. Synthesis of β-lactones 6 from lithium phenyl ester enolates 8 and carbonyl compounds 4

alkanoates 7 by treatment with lithium diisopropylamide (LDA) react with ketones 4 to α,α,β,β-tetrasubstituted or α,β,β-trisubstituted β-lactones 6 in 75–95 % yield. With aldehydes 4 (R^2 = H) α,α,β-trisubstituted or α,β-disubstituted β-lactones are obtained. The yields of the latter are significantly lower than those of the more substituted β-lactones obtained from ketones. With aldehydes as carbonyl compounds considerable amounts of the 1,3-dioxan-4-ones 9 are formed in a competitive side-reaction (ref. 8). These results parallel those obtained for the reaction of carbonyl compounds with lithium ester enolates 8 (SPh instead of OPh) derived from *S*-phenyl alkanethioates (ref. 9). Since the yields are comparable, the application of lithium phenyl ester enolates, however, seems to be the superior method. It avoids the handling of malodorous benzenethiol for the preparation of the *S*-phenyl alkanethioates and during the workup of the β-lactones.

α-Chloro-β-lactones from carbonyl compounds and phenyl α-chloroalkanoates by the Darzens reac-

tion. Since the synthesis of α,β-disubstituted β-lactones from lithium phenyl ester enolates and aldehydes was less efficient than that of the more substituted β-lactones, we investigated the reaction of carbonyl compounds and lithium phenyl ester enolates 12 derived from phenyl α-chloroalkanoates 11. This was done with the aim to obtain trisubstituted α-chloro-α,β-dialkyl-β-lactones 15 (R^2 = H) and to convert them into the desired α-monosubstituted β-lactones 16 by reductive removal of the chloro substituent (Scheme 3).

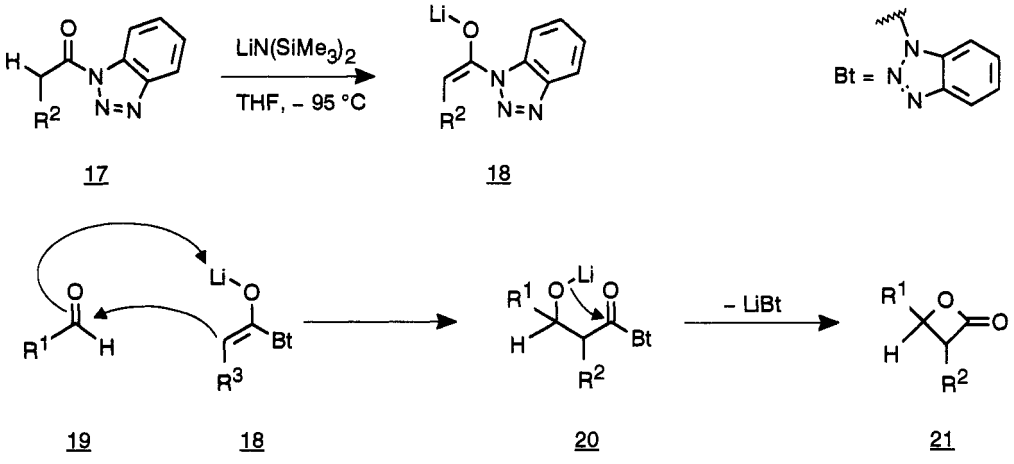


Scheme 3. Synthesis of α-chloro-β-lactones 15 by a Darzens reaction of phenyl ester enolates 12 and carbonyl compounds 4

This concept could be realized. The phenyl ester enolates 12 prepared from phenyl α-chloroalkanoates by treatment with lithium hexamethyldisilazanide form with the carbonyl compounds 4 the *O*-lithiated phenyl α-chloro-β-hydroxyalkanoates 14, which smoothly eliminate lithium phenolate and afford the α-chloro-β-lactones 15. Again, the yields obtained with ketones were higher than those obtained with aldehydes. However, it has to be pointed out that glycidic esters 13, the products of the conventional Darzens reaction of alkyl α-chloroalkanoates with carbonyl compounds, were not formed. Apparently, the elimination of lithium phenoxide from 14 is much more favoured than the elimination of lithium chloride (ref. 10). The removal of the α-chloro substituent of 15 was readily achieved by reduction with tributyltin hydride (ref. 11).

β-Lactones from carbonyl compounds and lithium amide enolates derived from 1-alkanoylbenzotriazoles. A common feature of the foregoing described novel β-lactone syntheses is the fact that the phenoxy residue in the intermediates 5, 10, and 14 is a good leaving group. It facilitates the attack of the electrophilic carbon atom of the activated ester group on the metalated β-hydroxy group of the intermediate and enables in this way the observed intramolecular acylation. In this connection the question arose whether there exist other active carboxylic acid derivatives, which are superior to the phenyl esters with regard to the yield of the obtained β-lactones and the diastereoselectivity of the carbon-carbon bond formation. In a screening of such activated carboxylic acid derivatives the 1-acylbenzotriazoles 17 revealed to be especially useful starting materials for a one-step β-lactone synthesis (Scheme 4). Deprotonation of the 1-acylbenzotriazoles 17 with lithium hexamethyldisilazanide at –95 °C and subsequent reaction of the thus generated lithium amide enolates 18 at this temperature with aldehydes 19 afforded the α,β-disubstituted β-lactones 21 in yields of 40–90 %. The ratio of the *cis* and *trans* diastereoisomers varies between 1 : 2.4 and 1 : 9 (ref. 12). The structure of the diastereoisomers was determined on the basis of their ^{1}H-NMR spectra. According to the literature (ref. 13) the coupling constants $J_{\alpha,\beta}$ of the protons of C_α and C_β of *cis* and *trans*

disubstituted β-lactones are about 6.5 and 4.5 Hz, respectively. The signal of the proton at C_α is always at higher field than the signal of the proton at C_β. In addition, the signal of a proton in a *trans* β-lactone is always at higher field than the signal of the corresponding proton of the *cis* isomer (ref. 14).



Scheme 4. Synthesis of α,β-disubstituted β-lactones 21 from lithium amide enolates 18 and aldehydes 19

CONCLUSIONS

It could be shown that aldol reactions of carbonyl compounds with enolates of activated carboxylic acid derivatives, such as phenyl esters or benzotriazolides, afford the corresponding *O*-metalated β-hydroxyalkanoic acid derivatives. Due to the enhanced electrophilicity of the ester or amide carbonyl group these intermediates spontaneously undergo an intramolecular acylation to β-lactones. The developed one-step procedures can well compete with other established β-lactone syntheses (ref. 15). The stereochemical problems of the described reactions are matter of forthcoming investigations.

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