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A modified Prins reaction for the facile synthesis of structurally diverse substituted 5-(2-hydroxyethyl)-3,3-dihydrofurane-2(3*H*)-ones

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ABSTRACT

Furanones are important synthetic intermediates commonly found in natural products, receptor ligands, and drug molecules. Unacceptable yields of substituted furanones obtained using a previously reported Prins reaction led to the development of a modified approach. Readily prepared substituted allylic esters were reacted under Prins reaction conditions catalyzed by a protic acid to provide structurally diverse substituted furanones in modest to good yields. The reaction goes through a protected caprolactone intermediate that was isolated and characterized for selected compounds. The approach supplies an efficient, versatile, and higher yield method for the synthesis of these important heterocyclic intermediates.

Substituted dihydrofuranones (or γ-butyrolactones; GBLs) are important synthetic intermediates in organic synthesis and are commonly found as fragments in natural products, receptor ligands, and drug molecules.[1] Furthermore, compounds containing a GBL moiety have a long history of pharmacological effects that include muscarinic (pilocarpine) [2] and antimuscarinic activity (Kaiser lactones),[3] convulsant (picrotoxin, β-substituted GBL) and anticonvulsant activity (α-alkyl substituted GBLs),[4] and more recently, the ability to modulate quorum sensing.[5] Our interest in the synthesis of a homologous series of lactone-based muscarinic ligands required an efficient route to 5-hydroxyethyl furanones with various substitutions at the 3 position (see Fig. 1). Although a number of methods for the synthesis of similar furanones have been reported,[3,6] high yield, and facile routes to the structurally diverse target intermediates are lacking.

Based on the retrosynthetic analysis shown in Figure 1, the modified Prins reaction was viewed as a practical route to the target intermediates. The starting allylic esters can be readily synthesized with a variety of α-substituents based on a previously published procedure.[7] In that work, the allylic ester was treated with paraformaldehyde under Lewis acid-catalyzed (boron trifluoride etherate) conditions to provide the desired lactone as a minor product (20% yield) and the corresponding ethyl ether as the major product (42%; See Scheme 1). Ether cleavage was accomplished by treating the ether with boron tribromide in dichloromethane (29% overall from the allylic ester).[8] Failed efforts to optimize these reaction conditions to improve efficiency prompted a re-examination of the approach in order to develop a more versatile, higher yield method.

The Prins reaction is a versatile reaction that provides a variety of products including 1,3-diols, 3-substituted alcohols, allylic alcohols, ethers, and 1,3-dioxanes.[9] A major drawback of the approach is the potential for unwanted side products that can result in low yields. Careful planning and precise control of the reaction conditions are critical in order to isolate high yields of the desired products. The well known mechanism for the Prins reaction and the products isolated in previous reports suggest that two major pathways may be involved in producing side products: (1) the carbocation intermediate reacts with unintended nucleophiles. (2) The resulting diol undergoes elimination or forms ethers under the acidic reaction conditions.

With these considerations in mind, a novel approach was developed using a protic acid rather than a Lewis acid. Acetic acid in the modified Prins reaction reported herein serves to capture the resulting carbocation (Fig. 2) to provide a protected hydroxyl group. The remaining aliphatic alcohol is also protected by an intramolecular esterification that occurs under these conditions. Based on this method, the reactive cation is captured as an acetate and the remaining hydroxyl is protected in the form of the caprolactone. Sequential treatment of the resulting seven-membered

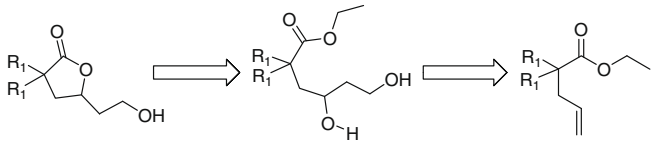

Figure 1. The Prins reaction as a potential route to the target furanones.

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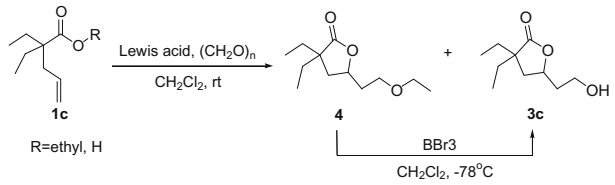


Scheme 1. Synthesis of 3,3-diethyl-5-(2-hydroxyethyl)dihydrofuran-2(3*H*)-one (**3c**) using a previously reported Prins reaction.

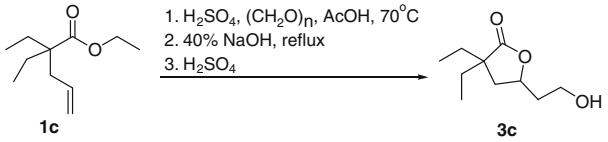
lactone with aqueous base and then acid affords the desired hydroxyethyl lactones (Table 2) in moderate to good yield.

The modified Prins reaction was first attempted with allylic ester **1c**. Hence, paraformaldehyde was treated with a catalytic amount of sulfuric acid in glacial acetic acid at 90 °C. Ester **1c** was then added and the mixture stirred at 70 °C for 12 h to afford the protected 1,3-diol intermediate. Treatment with aqueous NaOH followed by acidification with H_2SO_4 provided the target lactone–alcohol **3c** in 45% yield.

Efforts to optimize reaction conditions included the use of different molar ratios of acetic acid and various reaction times and temperatures (Table 1). For example, the synthesis of **3c** described above (yield = 45%) used a molar ratio of acetic acid = 10, and a reaction time of 12 h at 70 °C. The yields of **3c** were improved to 77% by increasing the molar ratio of acetic acid (reaction time and temperature remained constant). This observation may be attributed to a more efficient capturing of the carbocation in the presence of higher concentrations of acetic acid. Reactions times of 12 h are sufficient for the conditions tested herein since no improvement in the yield was observed with longer times.

To explore the scope of the reaction, allylic esters or acids with various substituents (**1a–g**) were investigated. Compounds **1a–g** are unsubstituted (**1a**) or contain aliphatic or aromatic groups at the α-carbon. These starting materials were readily prepared using previously published procedures[7,10] and afford the target lactone intermediates in moderate to good yields (see Table 2). These data indicate that the newly described modified Prins reaction is superior to the previous method for the synthesis of these substituted lactones. The esters and acids included in the present work have symmetrical substituents adjacent to the carbonyl (except **1a**) in order to avoid multiple chiral centers in the final lactones. Asymmetric centers are often kept to a minimum in drug discovery programs to simplify the interpretation of biological screening data However, the fact that unsubstituted compound **3a** was successfully prepared in modest yield suggests that the presence of a single substituent at the alpha position would lead to acceptable yields of alpha 'monosubstituted' lactones using the method reported herein.

Table 1
Synthetic route to 3,3-diethyl-5-(2-hydroxyethyl)dihydrofuran-2(3*H*)-one and reaction conditions attempted to optimize yield



Mole ratio of AcOH	Time (h)	Temperature (°C)	Yield[a] (%)
10	12	70	45
30	12	70	63
50	12	70	77
100	12	70	76
50	24	70	77
50	48	50[b]	67
50	12	90	74

[a] Isolated yield.
[b] Starting material was not consumed in 36 h (TLC). Temperature raised to 70 °C for additional 12 h after which starting material was fully consumed.

In order to confirm that the reaction goes through the seven-membered lactone intermediate proposed above, selected intermediates (**2a, 2c, 2d, and 2f**) were isolated, characterized, and yields were calculated (Table 2). The spectroscopic and analytical data for these compounds can be found in Supplementary data and are consistent with the seven-membered lactones shown in Figure 2.

The target lactones prepared using this approach may serve as key synthetic intermediates in a wide range of reactions (e.g., Mitsunobu, Sonogashira, Wittig, and substitution reactions). The versatility of the compounds makes them excellent fragments for parallel synthesis in drug discovery efforts where lactone moieties are of interest. In our hands, similar hydroxyethyl lactone precursors have been utilized to prepare amines, amides, carbamates, ethers, and esters.[7] Several of these compounds were found to exhibit anticonvulsant activity or to bind to muscarinic receptors. Using this improved method, several hydroxyethyl lactone intermediates reported herein have been used to prepare novel lactone-based ligands for muscarinic receptors. Screening of those ligands is underway and the results of those efforts will be reported elsewhere.

In summary, substituted furanones are an important class of heterocyclic compounds that find utility as synthetic intermediates in organic synthesis and are common components in numerous pharmacologically important ligands and drugs. A more efficient method for the preparation of substituted furanones has been developed wherein readily prepared allylic esters or acids are reacted under Prins reaction conditions catalyzed by a protic acid to provide structurally diverse substituted furanones in moderate

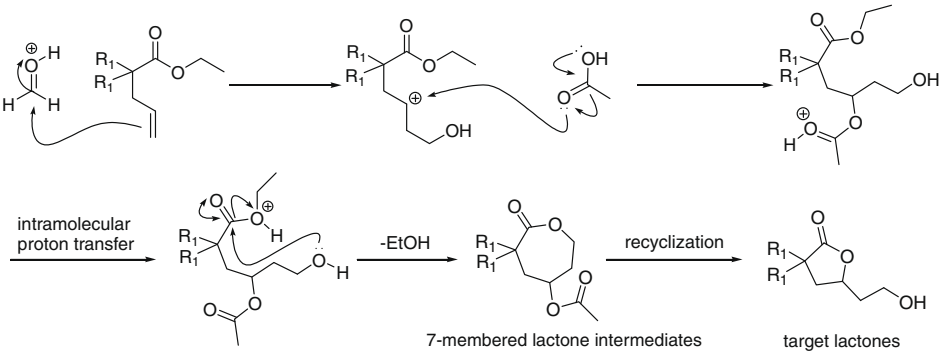
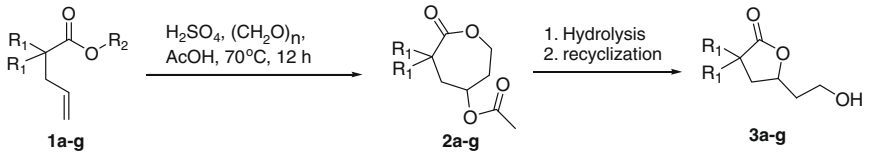


Figure 2. Proposed mechanism to target furanones via caprolactone intermediates.

Table 2
General synthetic route to intermediates (**2a**–**g**), target furanones (**3a**–**g**) and specific data pertaining to the individual compounds



1a-g **2a-g** **3a-g**

1a, 1d-g, R_2=H; **1b, c**, R_2=ethyl

R_1	Intermediate no.	Yields[a] (%)	Compd no.	Yield[a] (%)
H	**2a**	80	**3a**	43
Methyl	**NI**[b]	ND[c]	**3b**	81
Ethyl	**2c**	79	**3c**	76
Spiro (4)	**2d**	80	**3d**	74
Spiro (5)	**NI**	ND	**3e**	73
Spiro (6)	**NI**	ND	**3f**	73
Phenyl	**2g**	74	**3g**	66

[a] Yields based on starting allylic ester/acids.
[b] NI = Not isolated.
[c] ND = Yields not determined.

to good yields. The approach reported herein requires fewer steps and provides higher yields to a diverse series of heterocyclic compounds that will serve as useful synthetic fragments in a wide range of reactions.

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Supplementary data

Supplementary data (efforts to improve a previously reported Prins reaction; details of the modified method; ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.016.

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