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Mucohalic acid in Lewis acid catalyzed Mukaiyama aldol reaction: a concise method for highly functionalized γ-substituted γ-butenolides

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Abstract—The first Mukaiyama aldol reaction on mucohalic acid (**1a/b**) has been achieved. Reaction of **1** with various ketene silyl acetals or silyl enol ethers in the presence of a Lewis acid provides the γ-substituted γ-butenolides in good to excellent yield.

The great importance of substituted γ-butyrolactones (γ-butanolides or γ-lactones)[1] and α,β-unsaturated γ-lactones (γ-butenolides)[2] has attracted much attention for synthetic organic and medicinal chemists. Both γ-butyrolactones and γ-butenolides appear in a large variety of biologically active natural products, such as (−)-roccellaric acid,[3,4b] phaseolinic acid,[4] asimicin,[5a] bullatacin,[5a] squamotacin,[5b] trilobin,[5c] and enrollment as pharmaceuticals, for example, Vioxx[6] and endothelin antagonists.[7] Meanwhile, they are prominent moieties in the building of natural flavors and odors, including sex attractant pheromones of some species of insects,[8] which may prove beneficial for developing environmentally friendly insecticides. Furthermore γ-butenolides have been employed to make some functionalized open-chain molecules, such as 1,4-solfanylalcohols,[9] compounds found in fruits and vegetables and have been the subject of intense research in flavor chemistry. On the other hand, γ-butyrolactones also serve as precursors to fused bicyclic lactones, such as dihydrocanadensolide, isoavenociolide, ethisolide,[10] and avenaciolide.[10,11] Mucohalic acids **1a/b** (Fig. 1) are two highly functionalized molecules and can be viewed as α,β-unsaturated aldehydes and pseudo unsaturated γ-lactones which make them ideal as the building blocks to access highly functionalized γ-substituted γ-butenolides.[12]

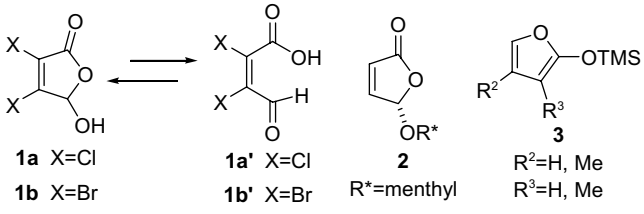

Figure 1. Mucohalic acid (**1**) and some related compounds used in Mukaiyama aldol reaction.

It is unlikely for the Grignard reagents attacking the aldehyde C=O functional group of mucohalic acid to form the γ-substituted γ-butenolides since the other functional groups, vinyl halides are sensitive to nucleophiles.[13] Additionally, it is very unlikely to apply the classic aldol reaction to **1a/b**, the base catalyzed condensation of one carbonyl compound with the enolate/enol of another, to generate a γ-butenolide since mucohalic acids have poor stability under basic conditions. Understanding the stability issues of mucohalic acid allowed us to rapidly focus our attention to investigate the Lewis acid catalyzed Mukaiyama aldol reaction.[14] We reasoned these conditions would enable aldehyde C=O bond activation and its aldol reaction rather than the nucleophilic replacement of the halogen atoms in α- or β-positions. To our best knowledge, there are very few reports regarding the use of this approach to form γ-butenolides. van Oeveren and Feringa[15a] reported the asymmetric synthesis of γ-substituted γ-butenolides via Mukaiyama aldol type reaction where

Keywords: Mucohalic acid; Mukaiyama aldol; Butenolides; Lewis acid.
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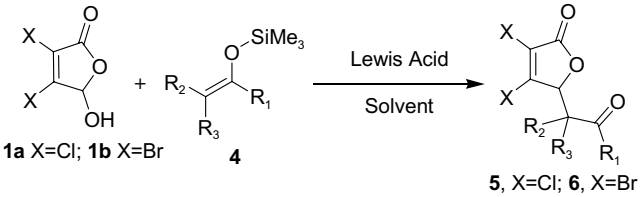
5(*R*)-(menthyloxy)-2(5*H*)-furanone **2** was the chiral synthon; Evans et al.[15b] described the synthesis of enantiomerically pure γ-substituted γ-butenolides using siloxyfuran **3** and C_2-symmetric Cu(II) complexes. van der Ohe and Brückner reported a Mukaiyama aldol addition/anti-elimination route to γ-alkylidenebutenolides where siloxyfuran **3** was the starting material (Fig. 1).[16]

In this letter, we describe our results of Lewis acid catalyzed Mukaiyama aldol reaction where mucohalic acids **1a/b**, inexpensive and commercially available starting materials act as aldehydes (Scheme 1). Having easy access to γ-substituted γ-butenolide with α- and β-activated functional groups should enable the preparation of potentially more complex molecules containing this skeleton.

Mucohalic acid **1a/b** can exist either as the open or cyclic form; however, it is accepted and confirmed that **1** exists predominantly in the lactone form. Thus, the Lewis acid-promoted reaction between ketene silyl acetal (KSA) or silyl enol ether (SEE) and mucohalic acid can be viewed as a nucleophilic reaction of a hemiacetal.

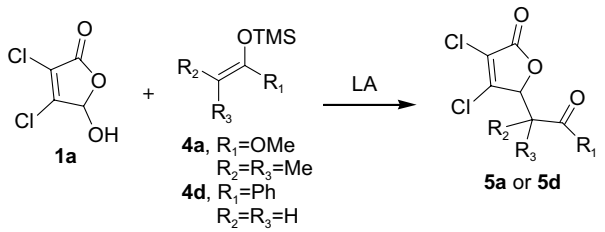
Lewis acid screening work was carried out using methyl trimethylsilyldimethyl ketene acetal **4a** for a representative KSA and the SEE 1-phenyl-1-(trimethylsilyloxy)ethylene **4d**. These two nucleophiles were chosen because both are commercially available. Initial application of Mukaiyama-aldol conditions toward mucochloric acid (**1a**) led to a key observation—the reaction is catalyzed by Lewis acid in substoichiometric levels. The catalyst screening for the representative KSA is shown in Table 1. Among the Lewis acids screened, $ZnCl_2$ and $Sc(OTf)_3$ were superior providing 88% and 84%, respectively, of the desired lactone **5a**.[17] Three other catalysts, $Sn(OTf)_2$, $TiCl_4$, and $Zn(OTf)_2$ provided 70%, 58%, and 52% of **5a**, respectively. Although the remaining catalysts, provided small amounts of **5a**, they were not synthetically useful at this substoichiometric level.[18]

Surprisingly, $ZnCl_2$ is not an efficient catalyst for the reaction between SEE **4d** and mucohalic acid, providing only 43% product **5d**. The result of the catalyst screening for SEE **4d** (see Supporting material) shows that $Sc(OTf)_3$ was superior providing 79% of the desired lactone **5d**. Other catalysts, $InCl_3$ and $Sn(OTf)_2$, provided **5d** in 64% and 61% yield, respectively. The remaining catalysts were inferior at this substoichiometric level. Based on these results, we decided to use $ZnCl_2$ as the Lewis acid when KSA was the nucleophile and $Sc(OTf)_3$ when SEE was used.



Scheme 1. Mukaiyama aldol reaction on mucohalic acid.

Table 1. Mukaiyama aldol reaction-Lewis acid study[a]



Entry (**1a**+**4a**)	Catalyst	**1a**[b]	**5a**[b]
1	$La(OTf)_3$	92	3
2	$Mg(OTf)_2$	95	1
3	$Sc(OTf)_3$	14	84
4	$TiCl_4$	39	58
5	$ZnCl_2$	7	88
6	$Zn(OTf)_2$	41	52
7	$InCl_3$	89	7
8	$Sn(OTf)_2$	28	70
9	$BF_3{\cdot}OEt_2$	72	17
10	None	*	ND
11	$Pd(CF_3CO_2)_2$	97	1

* Only silylated **1a** was observed.

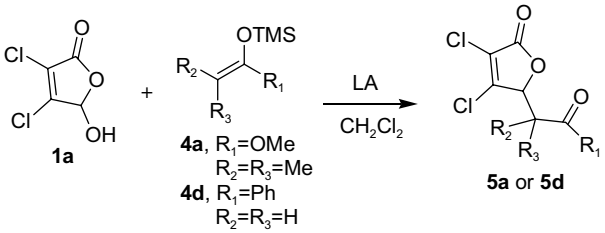
[a] Reaction conditions: 1 mmol scale; 0.25 M in PhMe (KSA) or Et_2O (SEE), 2.0 equiv **4**, 10 mol % catalyst; reactions were stirred at −20 °C for 2 h then at rt for 3 h.

[b] Yield was determined by HPLC (215 nm). ND (none detected).

In order to find appropriate and reliable conditions for the Mukaiyama aldol reaction on mucohalic acid **1a/b**, further studies were undertaken to determine two other reaction parameters: temperature and solvent. Since $ZnCl_2$ and $Sc(OTf)_3$ were shown to be highly effective catalysts in initial screening experiments they were used in determining the temperature/solvent semi-optimization conditions.

The result of the temperature screen showed very little effect from $-30 < T < 20$ °C for either KSA or SEE (Table 2). Only slightly better conversions were observed

Table 2. Mukaiyama aldol with KSA/SEE-temperature study[a]

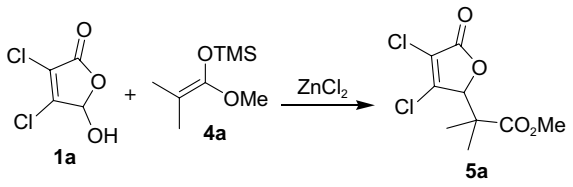


Entry	T (°C)	**5a**[b] (%)	Entry	T (°C)	**5d**[b] (%)
1	−30	94	6	−30	78
2	−10	94	7	−10	78
3	0	92	8	0	77
4	10	89	9	10	74
5	20	84	10	20	73

[a] Reaction conditions: 1 mmol scale; 0.25 M (CH_2Cl_2), 2.0 equiv **4**, 10 mol % $ZnCl_2$ (**4a**) or $Sc(OTf)_3$ (**4d**), 16 h.

[b] Yield was determined by HPLC and represents the total conversion of **1a** to **5** and its presumed hydrated open form (*seco*-acid form; 0–8%) after 16 h.

Table 3. Mukaiyama aldol with KSA-solvent study[a]



Entry	Solvent	**1a**[b] (%)	**5a**[b,c] (%)
1	PhMe	6	94
2	Et_2O	6	94
3	THF	76	24
4	CH_2Cl_2	8	92
5	$CHCl_3$	29	71
6	$MeNO_2$	3	>96
7	EtCN	56	44
8	DME	33	67

[a] Reaction conditions: 1 mmol scale; 0.25 M, 2.0 equiv **4a**, 10 mol % $ZnCl_2$; reactions were stirred at −20 °C for 2 h then at rt for 14 h (no further consumption of **1a** was observed with longer reaction time).
[b] Yield was determined by HPLC (215 nm).
[c] Represents the total conversion of **1a** to **5** and its presumed hydrated open form (0–8%).

at $-30 < T < 0$ °C. With this data we determined to complete the remainder of the study at −20 °C for both the KSA's and the SEE's.

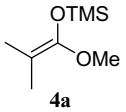
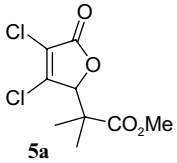
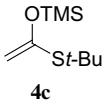
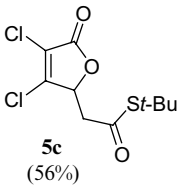
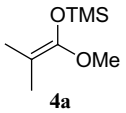
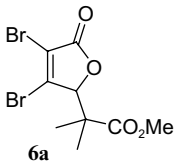
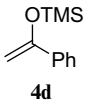
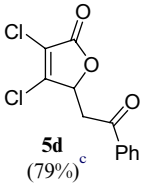
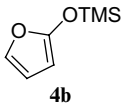
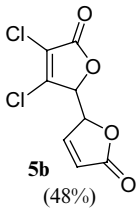
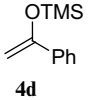
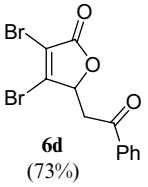
During the Lewis acid catalyst screen, we observed that $ZnCl_2$, $InCl_3$, and $Sn(OTf)_2$ showed essentially no reaction at $T = -20$ °C with **1a** and **4d**; however, HPLC analysis after 16 h at rt showed significant amounts of lactone **5d** were produced. This observation, in contrast to the $Sc(OTf)_3$ result, clearly indicates that temperature optimization is catalyst dependant.

After finding suitable temperature conditions, a solvent screen was initiated (Table 3). In the case of KSA **4a**, four of the eight solvents screened—PhMe, Et_2O, CH_2Cl_2, and $MeNO_2$ gave excellent results with conversions of 92% or higher. Although $MeNO_2$ provides the fastest/highest conversion (1 h at −20 °C provided >96% conversion), for environmental and safery reasons, PhMe (94% conversion) was chosen to complete the subsequent substrate study. Moderate-performing solvents include $CHCl_3$ and DME (71% and 67% conversion, respectively) while EtCN and THF are poor-performing solvents (44% and 24% conversion, respectively).

The SEE solvent screen provided similar results (see Supporting material). Again, PhMe, Et_2O, CH_2Cl_2, and $MeNO_2$ were found to be the best-performing solvents with 72–83% conversions; Et_2O provided the highest production of **5d** and was used in the substrate study. Mid-performing solvents were $CHCl_3$ and DME. They provided 62% and 43% of **5d**, respectively; however, EtCN is a poor-performing solvent providing only 8% of **5d** with 13% of a double-aldol product. THF is incompatible with $Sc(OTf)_3$.

Finally, using the semi-optimized reaction conditions (temperature, solvent, and Lewis acid) mucohalic acid was treated with various KSA's (**4a–c**) and SEE **4d** to explore the generality of the reaction (Table 4). All provide the expected lactones **5a–d**, **6a**, and **6d** in moderate to good yields. The reactions are generally clean, but some difficulty is encountered in obtaining complete consumption of mucohalic acid **1a/b**; this obstacle is likely a result of silylation of **1a/b** before the reaction occurs.

Table 4. Mukaiyama aldol with KSA and SEE[a]

KSA	Product (yield)[b]	KSA/SEE	Product (yield)[b]
 **4a**	 **5a** (80%)	 **4c**	 **5c** (56%)
 **4a**	 **6a** (75%)	 **4d**	 **5d** (79%)[c]
 **4b**	 **5b** (48%)	 **4d**	 **6d** (73%)

[a] Reaction conditions: 1 mmol scale; 0.25 M in PhMe (**4a–c**) or Et_2O (**4d**), 2.0 equiv **4**, 10 mol % $ZnCl_2$ (**4a–c**) or $Sc(OTf)_3$ (**4d**); reactions were stirred at −20 °C for 2 h then at rt for 16 h.
[b] Isolated yield; products passed elemental analysis or HRMS.
[c] A 35 mmol scale also provided **5d** in 79% yield.

Using this method, butenolide **5b**, a core structure found in some important natural products, such as biatractylolide, biepiasterolide, and others,[19] was prepared. Without purification, **1a** and **2b** gave predominantly (90%) *syn*-**5b** and 10% *anti*-**5b**.[20] After crystallization, NMR analysis indicated a single stereoisomer; X-ray crystal structure analysis of **5b** confirmed the *syn* racemate (Fig. 2).

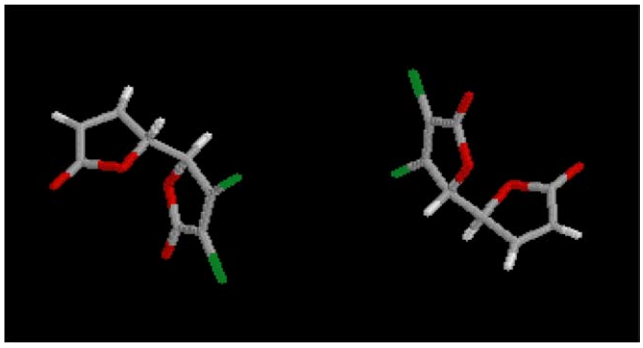


Figure 2. X-ray crystal structure for γ-butenolide **5b**.

Unlike the normal Mukaiyama aldol reaction that generates a β-hydroxy carbonyl compound, this approach gives predominantly the γ-butenolides as the product. Therefore, the possible mechanism (see Supporting material) is more complicated since two carbonyl groups in mucohalic acid may be activated. Meanwhile, both cyclic and open forms of mucohalic acid are likely involved in the formation of final γ-butenolides.

This latest methodology has several advantages: (1) both starting materials are cheap, commercially available or easily prepared; (2) the reaction occurs under mild conditions with good to excellent yield; (3) the products are highly functionalized, allowing further transformation; (4) since the Lewis acid requirement is catalytic (10% or lower)[21] practical asymmetric Mukaiyama aldol reaction conditions offer opportunity to prepare optically-active γ-butenolides.[22]

In summary, we have developed a simple, efficient, and selective method to prepare a variety of highly functionalized, γ-substituted γ-butenolides using the Mukaiyama aldol reaction. Further investigations, including extension of the use of these synthons will be reported in due course.

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Supplementary data

Supplemetary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.147.

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17. The overall desired aldol reaction may be slightly higher—for simplicity of discussion, any remaining uncyclized *seco*-acid (0–8%) is not reported in Table 1.
18. Interestingly, a separate experiment using a stoichiometric amount of $BF_3{\cdot}OEt_2$ provided nearly quantitative yields of lactone **5a**.
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20. This result is in agreement with other published work; for example, see: Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375, and references cited therein.
21. Experiments using as low as 5 mol % LA also provided good yield of **5a**; however, the ring-closing event was slower.
22. Using a Lewis acid/chiral ligand we have obtained **5d**, without purification, in 79% ee; unpublished result.