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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]

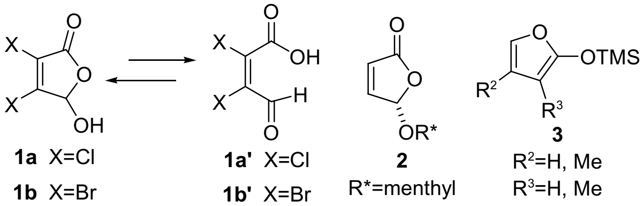

Figure 1. Mucohalic acid (**1**) and some related compounds used in Mukaiyama aldol reaction.

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

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Keywords: Mucohalic acid; Mukaiyama aldol; Butenolides; Lewis acid.

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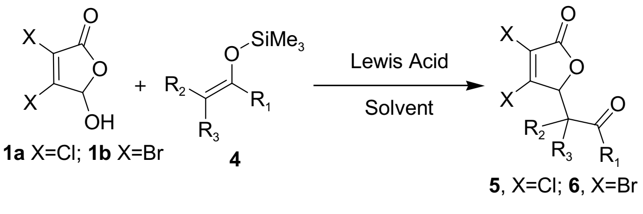
5(*R*)-(menthyloxy)-2(5*H*)-furanone **2** was the chiral synthon; Evans et al.[15b] described the synthesis of enantiomerically pure γ-substituted γ-butenolides using siloxyfuran **3** and C_2-symmetric Cu(II) complexes. van der Ohe and Brückner reported a Mukaiyama aldol addition/anti-elimination route 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.

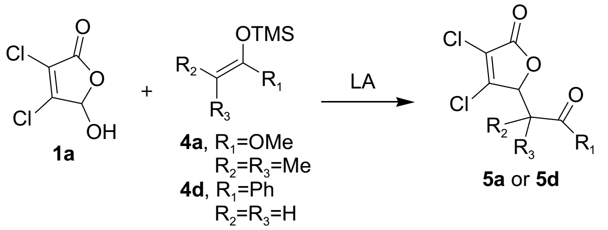
Lewis acid screening work was carried out using methyl trimethylsilyldimethyl ketene acetal **4a** for a representative KSA and the SEE 1-phenyl-1-(trimethylsilyloxy)ethylene **4d**. These two nucleophiles were chosen because both are commercially available. Initial application of Mukaiyama-aldol conditions 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.

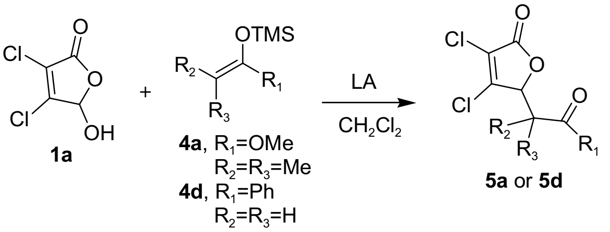
[a] Reaction conditions: 1 mmol scale; 0.25 M in PhMe (KSA) or Et_2O (SEE), 2.0 equiv **4**, 10 mol % catalyst; reactions were stirred at −20 °C for 2 h then at rt for 3 h.

[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.