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COMMUNICATION

Gallium-Catalyzed Reductive Lactonization of γ-Keto Acids with a Hydrosilane

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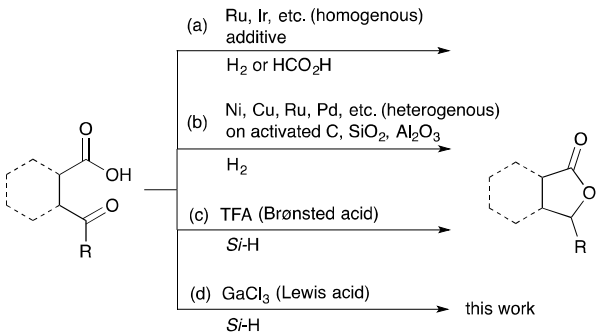
Described herein is the $GaCl_3$-catalyzed lactonization of γ-keto carboxylic acids in the presence of $PhSiH_3$ leading to the direct preparation of γ-lactone derivatives. This reducing system showed a relatively wide functional group tolerance.

Since γ-lactone derivatives constitute a central and ubiquitous structure in valuable natural products and biologically active substances, the development of a facile approach to these skeletons has attracted the interest of a number of organic, pharmaceutical and material chemists.[1] Thus far, a typical approach to the γ-lactone skeleton has been generally achieved through cyclization of a carboxylic acid bonding an alcohol moiety (γ-hydroxy acid) in the presence of a variety of condensation reagents.[2] Also, the lactonization of ω-hydroxy acid by a sole metal triflate, $Hf(OTf)_4$, has been reported.[311] Moreover, a cyclization of 1,4- or 1,5-keto alcohols using a Noyori hydrogen transfer catalyst led to the asymmetrical synthesis of γ-lactone.[4]

On the other hand, as a recent interesting extension, the preparation of a γ-lactone skeleton through a reductive lactonization from a biomass-derived γ-keto carboxylic acid, such as levulinic acid (LA), to γ-valerolactone (GVL), has been disclosed gradually. For example, as with cases involving a homogenous metal catalyst, a $RuCl_3$-PPh_3 system[5] or a $Ru(acac)_3$ complex,[6] the Shvo complex,[7] and an Iridium pincer complex[8] with an additive, these have efficiently reduced LA to GVL in the presence of H_2 or HCO_2H as a reducing reagent (eq a in Scheme 1). Also, the same transformation with heterogeneous complexes such as Ni, Raney-Ni, Cu, Ru, and Pd supported on either activated carbon, SiO_2, or Al_2O_3, under hydrogen gas has been developed (eq b in Scheme 1).[9] Moreover, as an alternative reducing reagent, the use of easily-handled hydrosilanes has been reported. For example, Doyle[10] and Rovis[11] disclosed that a cyclic γ-keto acid embedded in a ring structure was treated with trifluoroacetic acid (TFA)-Et_3SiH or TFA-$PhMe_2SiH$ to form a trisubstituted γ-lactone (eq c in Scheme 1). Although the reductive cyclization of a γ-keto carboxylic acid derivative with a Lewis acid, BF_3 and Et_3SiH was reported by Nordlander and co-workers, the example reported in this paper is the only one example of its kind, and a systematic investigation has not yet been conducted.[12] In addition, as an example of a two-step transformation, the combination of an initial reduction of 3-benzoylpropanoic acid by either a chiral borane[13] or $ZnCl_2$-$^{i}Bu_2AlH$[14] and subsequent cyclization with TFA led to the corresponding γ-lactone.

In this context, we reported the indium-catalyzed annulation of LA with aromatic/aliphatic amines in the presence of $PhSiH_3$ leading to the preparation of γ-lactam derivatives,[15] and found that a $GaCl_3$-TMDS (1,1,3,3-tetrahydrosiloxane)-$CuCl_2$ system undertook the reductive chlorination of carboxylic acids.[16] We report herein a gallium(III)-catalyzed reductive cyclization of γ-keto carboxylic acids with $PhSiH_3$ smoothly leading to γ-lactone derivatives (eq (d) in Scheme 1). This procedure using the novel association of a metallic Lewis acid, $GaCl_3$, and a hydrosilane, $PhSiH_3$, presents a new entry to a lactone skeleton from a keto carboxylic acid.[17]



Scheme 1 Diverse approaches to γ-lactones from γ-keto acids

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† Electronic Supplementary Information (ESI) available: Spectral data and ^{1}H- and ^{13}C-NMR charts of γ-lactones prepared by the present method. See DOI: 10.1039/x0xx00000x

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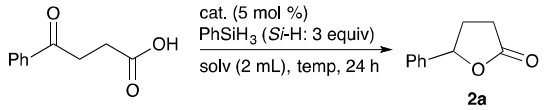
To achieve this concept, the reaction conditions were initially examined (Table 1). On the basis of our previous results,[15] when keto acid **1a** was treated with $In(OAc)_3$ (5 mol %) in the presence of $PhSiH_3$ (3 equiv) in toluene at 80 ˚C, the reductive cyclization slightly proceeded to produce 4-phenyl-γ-butyrolactone (**2a**) in a 23% yield (entry 1). Thus, although the effect of a counter anion on the indium compound was examined, a remarkable improvement in the product yield was not observed (entries 2-5). Interestingly, $GaCl_3$, instead of an indium compound, efficiently catalyzed the reductive cyclization (entry 6). On the other hand, other Lewis acids, such as $AlCl_3$, $ZnCl_2$, and $BiCl_3$, did not show an effect for this cyclization (entries 7-9). Thus, with a gallium halide in hand, when several examinations for solvents and temperatures were performed,[18] the heating conditions at 60 ˚C in the presence of $GaCl_3$ showed the best results (entries 10 and 11). Also, the use of a stronger Lewis acid, $GaBr_3$ and GaI_3, than $GaCl_3$ caused a decrease in the chemical yield (entries 12 and 13).

Table 1 Examinations of reaction conditions

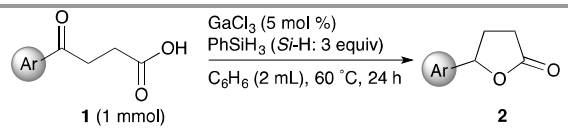


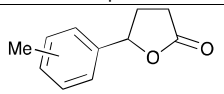
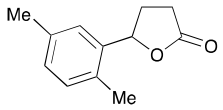
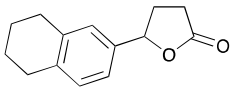
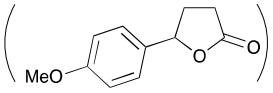
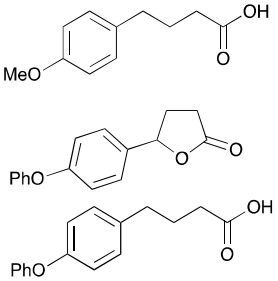
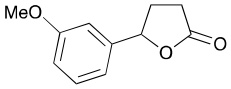
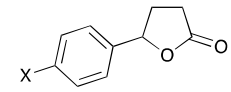
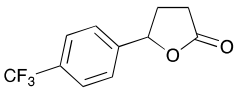
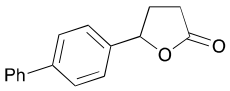
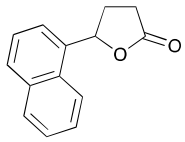
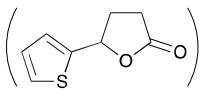
Entry	Cat.	Solvent	Temp (˚C)[a]	Yield (%)[b]
1	$In(OAc)_3$	toluene	80	23
2	$In(OTf)_3$	toluene	80	28
3	InI_3	toluene	80	31
4	$InBr_3$	toluene	80	20
5	$InCl_3$	toluene	80	34
6	$GaCl_3$	toluene	80	59
7	$AlCl_3$	toluene	80	0
8	$ZnCl_2$	toluene	80	0
9	$BiCl_3$	toluene	80	0
10	$GaCl_3$	benzene	80	82
11	**$GaCl_3$**	**benzene**	**60**	**99 (94)**
12	$GaBr_3$	benzene	60	74
13	GaI_3	benzene	60	69

[a] Bath temperature. [b] NMR (Isolated) yield.

Then, the effect of an aryl group on the keto acid was examined under the optimal conditions (Table 2). Regardless of location and number, the cases with a methyl-substituted aryl group gave lactones **2b-f** in relatively good yields. In contrast, keto acid **1g** having a *para*-MeO group did not cyclize, and instead, led to a formation (21%) of the carboxylic acid derivative **2g'**, the ketone moiety of which was reduced. This may be due to the fact that the indium compound would prefer to activate the methoxy group than the carbonyl moiety. Also, this result is not in complete agreement with the result shown by Nordlander *et al*, in which the TFA-Et_3SiH system selectively reduced only the ketone moiety of the keto acid.[12]

Table 2 Scope of an aryl group in keto acids **1**



Entry	product		Yield (%)
1		**2b** (*o*-Me)	86
2		**2c** (*m*-Me)	95
3		**2d** (*p*-Me)	90
4		**2e**	78
5		**2f**	97
6		**2g**	0
7		**2h**	72
		2h'	4
8		**2i**	84
9		**2j** (X = F)	76[b]
10		**2k** (X = Cl)	63[b]
11		**2l** (X = Br)	67[b]
12		**2m**	63
13		**2n**	72
14		**2o**	78
15		**2p**	0

[a] Isolated yield. [b] Reaction time = 7 d.

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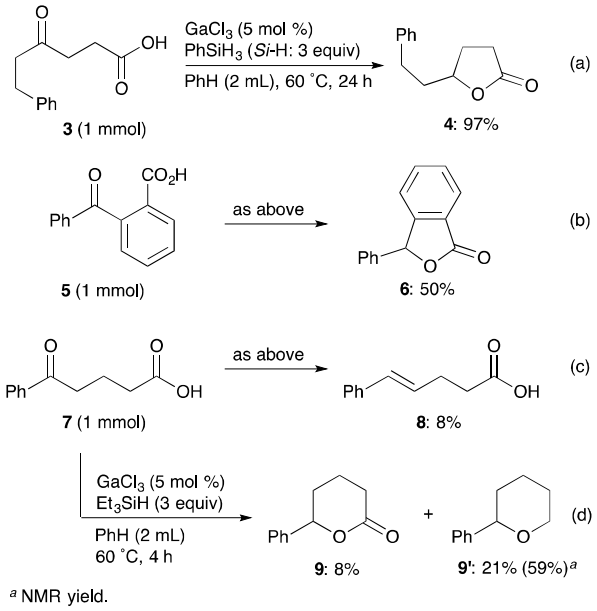
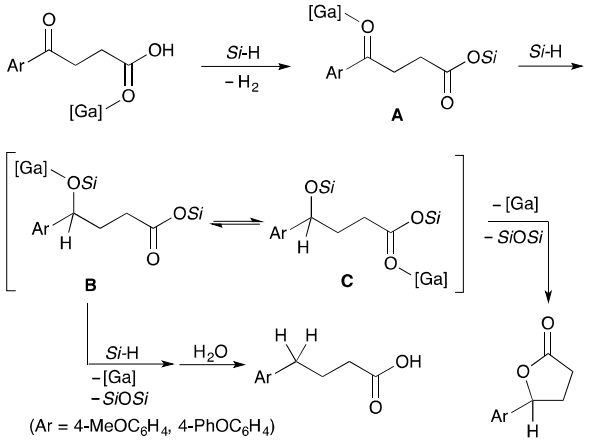
In contrast, the substrate having a *para*-PhO group afforded the corresponding lactone **2h** in a 72% yield with a by-product, the carboxylic acid **2h'** (4%). Moreover, the keto acid with a *meta*-MeO group successfully produced lactone **2i** in a good yield. Keto acids with a halogen substituent also gave the corresponding lactones **2j-2l** in relatively good yields, but a quite longer reaction time (> 7 days) was required to complete the cyclization. Consequently, a typical halogen atom in the aromatic ring shows a tolerance to the reducing system. On the other hand, the substrates with a CF_3, a biphenyl, and a 1-naphthyl group were mostly complete after 24 h, affording lactones **2m-2o** in 63, 72, and 78% yields. Unfortunately, instead of a benzene ring, the keto acid with a thiophene ring did not produce the expected lactone.



Scheme 2. Extension to various γ-keto carboxylic acids

As an extension, the present reducing procedure was applied to the lactonization of various γ-keto acids. For example, when keto acid **3** with an alkyl ketone moiety was treated with the optimal conditions, the expected cyclization proceeded cleanly to produce γ-phenethyl-substituted lactone **4** in a nearly quantitative yield (Eq a in Scheme 2). Then, when the cyclization was attempted with 2-benzoylbenzoic acid (**5**), 3-phenylphthalide (**6**) was obtained in a 50% isolated yield (Eq b in Scheme 2). To expand the ring size of the lactone skeleton, the similar lactonization with δ-keto carboxylic acids **7** was examined with the above optimal conditions. However, contrary to our expectation, the lactonization did not proceed cleanly, and, instead, the result was the production of carboxylic acid **8** with a *trans*-alkene portion (J = 16 Hz) in a low yield (Eq c in Scheme 2) and a complex mixture. Thus, when the same reaction was treated with Et_3SiH, the formation of δ-lactone **9** was isolated in a rather low yield, and an over-reduced 2-phenyltetrahydropyran (**9'**) was obtained in a 59% NMR yield as a major product (Eq d in Scheme 2). Although there is no clear reason for the over-reduction at this stage,[19] the reducing system could be applied to the 6-membered lactone construction.



Scheme 3 Plausible mechanism for the lactonization

Scheme 3 shows a plausible mechanism for the reductive lactonization from keto acids. As an initial step, the formation of silyl ester **A** via dehydrogenation between a carboxylic acid moiety activated by the indium catalyst and a hydrosilane occurred.[20] The second step is the hydrosilylation of the ketone moiety of the intermediate **A** to produce the anticipative intermediate **B** (or **C**). Subsequent intramolecular cyclization of the intermediate finally leads to the production of the expected γ-lactone.[21] In the cases with a strong electro-donating group, such as a 4-MeO or a 4-PhO substituent, on the aryl group, it seems that an electron-donating effect of these groups would promote the facile release of the silyl ether moiety activated by the gallium catalyst on **B**, and then the benzyl position was again reduced to produce the corresponding carboxylic acid.

We have developed a novel gallium(III)-catalyzed lactonization of γ-keto acids in the presence of $PhSiH_3$, which led to the production of γ-lactone derivatives with a variety of substituents, and showed that unlike a $GaBr_3$-TMDS reducing system[17a] and an In(III)-hydrosilane reducing system,[22] this reducing system involving $GaCl_3$ and $PhSiH_3$ in benzene retained the formed ester moiety. The present lactonization cleanly proceeds under relatively mild and neutral conditions.

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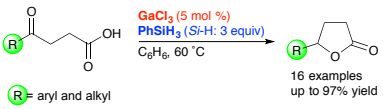

R = aryl and alkyl

Gallium chloride efficiently catalyzes cyclization of γ-keto carboxylic acids in the presence of $PhSiH_3$ to produce the corresponding γ-lactone derivatives.