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Lewis and Brönsted acid catalyzed Friedel–Crafts hydroxyalkylation of mucohalic acids: a facile synthesis of functionalized γ-aryl γ-butenolides

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Abstract—A catalytic, green and practical method for Friedel–Crafts hydroxyalkylation of mucohalic acid has been accomplished. Reaction of mucohalic acids with various electron-rich aromatic compounds in the presence of catalytic (1 mol % to 10 mol %) $In(OTf)_3$ or Brönsted acid, such as H_2SO_4 in acetic acid provides γ-aryl γ-butenolides in moderate to excellent yield.

The Friedel–Crafts acylation is one of the most important reactions for C–C bond formation in organic chemistry and widely utilized in the pharmaceutical industry.[1] The classical method generally requires using Lewis acids, such as $AlCl_3$, $ZnCl_2$, $TiCl_4$, or BF_3, to promote this reaction.[2] There are several disadvantages usually associated with this reaction: (1) The use of excess Lewis acid results in 'exciting' quenches, and significant heat generated in the decomposition of the complex, thus also making it impossible to recycle the Lewis acid. (2) These reactions are commonly carried out under anhydrous conditions, requiring the solvent and starting material to be pre-dried, which adds to time and money because most of Lewis acids are moisture sensitive. (3) The Lewis acids cited above often require halogenated or environmentally harmful and potentially hazardous solvents, such as CH_2Cl_2, $CHCl_3$, or CS_2, which create significant waste and it is oftentimes not cost effective. While a few significant catalytic Friedel–Crafts acylation reaction systems have been recently developed,[3] there remains room to improve yield, extend scope, reduce catalyst loading,[4] or use of green solvents.[5] Although catalytic Lewis acid processes have been developed, the use of co-catalysts, such as $AgClO_4$ and/or $LiClO_4$, was required. In the continued study of mucohalic acid chemistry, we decided to develop a green version of the Friedel–Crafts hydroxyalkylation to access substituted γ-aryl γ-butenolides.

Some naturally occurring furofuran lignans (Fig. 1) are substituted γ-aryl γ-butyrolactones with one or several phenolic structures. Recently the structural similarity of lignans with L-ascorbic acid (Vitamin C) prompted the suggestion that lignans be considered as natural phenolic antioxidants, like green tea with EGCG,[6] and viewed as health-promoting substances. It is the general opinion that the dietary intake of these antioxidants is associated with a lower risk of age-related health problems including cancer and coronary heart diseases.[7] Recently, Eklund et al.[8] reported their study results of antioxidant mechanisms and free radical scavenging properties of lignans. The SAR (structure–activity relationship) study indicated lignans showed a good radical scavenging capacity, and seem to be promising antioxidants, mainly due to their good stability. When compared to the known standard, such as Vitamin C, Vitamin E and BHT, some of these lignans showed an equally good or even better radical-scavenging capacity. Their most important finding is that those lignans showed a relatively slow kinetic profile, which may be useful as pharmaceutical products since the long-lasting antioxidant efficiency is crucial.

Several bislactones such as styraxin **1**[9] and eupomatilone **2**[10] have been synthesized and studied because of their broad range of biological activities such as antitumor[11]

Keywords: Friedel–Crafts hydroxyalkylation; Mucochloric acid; Mucobromic acid; Indium(III) salt; Green chemistry.
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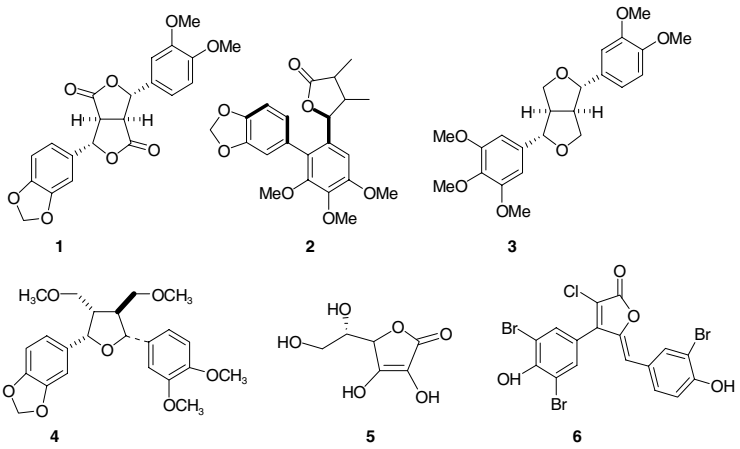
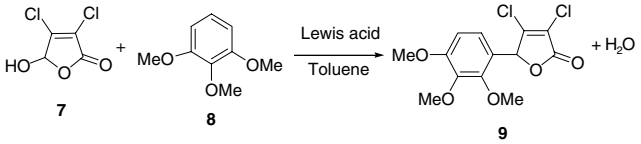


Figure 1. Some naturally occurring lignans, butenolides, substituted THF and L-ascorbic acid (**5**, vitamin C, antioxidant).

and anti-HIV properties.[12] Furthermore, aryl γ-butenolides can be used to synthesize substituted tetrahydrofurans, such as diaryl THF **3** and **4** via reduction.[13] We reasoned that mucohalic acids would be ideal to access aryl γ-butenolides since they are functionalized pseudo butenolides which are stable under acidic conditions.

There were also limited reports that used unsaturated aldehydes as the electrophile in Friedel–Crafts hydroxyalkylation (acylation).[14] Mucohalic acid can be viewed as an electron deficient unsaturated aldehyde;[15] thus choosing an electron-rich aromatic would build a better donator–acceptor relationship between these two reagents, which we suspected would be ideal for the reaction. Since we planned to use electron-rich aromatics, such as di- or trimethoxybenzene as reactants which would provide phenolic or anisolic substructures, classical strong, oxophilic Lewis acids, such as $AlCl_3$, $TiCl_4$, were removed from the screening list because these Lewis acids make a catalytic process impossible.[16] Since water will be formed in the reaction, a water stable, green, Lewis acid, such as $In(OTf)_3$ and $InCl_3$, became our first choice.[17]

We initially surmised that removing water from the reaction mixture would shift the equilibrium toward the product. We initially believed that the azeotropic removal of water using a Dean–Stark trap and toluene as the solvent maybe necessary, and would be simple. It was found that no reaction between mucohalic acid and toluene occurred under In(III) salt and thus toluene was used as solvent when 1,2,3-trimethoxybenzene reacted with mucohalic acid.[18]



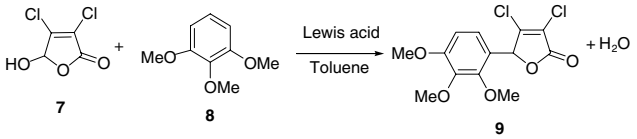
Scheme 1. Lewis acid catalyzed hydroxyalkylation of 1,2,3-trimethoxybenzene with mucochloric acid.

The initial experiment was encouraging. After heating a mixture of mucochloric acid and 1,2,3-trimethoxybenzene with 2.5 mol % $In(OTf)_3$, the color of the reaction mixture changed to purple. This color switch turned out to be a good indicator for a successful reaction. After 16–18 h at reflux, product **9** was isolated in 47% yield as the sole product. With this result in hand, we decided to screen a number of Lewis acids (Scheme 1).

Among several Lewis acids that were studied, their catalytic activities were found in the order: $In(OTf)_3 > Sn(OTf)_3 > Sc(OTf)_3 \gg Mg(OTf)_2 > InCl_3 > Zn(OTf)_2$. But $Yb(OTf)_3$, $BiCl_3$, $SnCl_2 2H_2O$, and $ZnCl_2$ did not show their efficiency as catalysts for this reaction. Having identified $In(OTf)_3$ as an ideal catalyst, we then determined the appropriate loading (Table 1) and found that the optimal catalyst level seemed to be 5–10 mol % (entries 1 and 2) and water removal was not required (entry 2).

It was also observed that although 1.0 equiv of 1,2,3-trimethoxybenzene and 1.0 equiv mucohalic acid was used, a small amount of mucohalic acid remained, while

Table 1. $In(OTf)_3$ loading study



Entry	$In(OTf)_3$ (mol %)	Conversion (%)
1	10	88[a]
2	5	76
3	2.5	47[a]
4	1	37
5	0.5	23

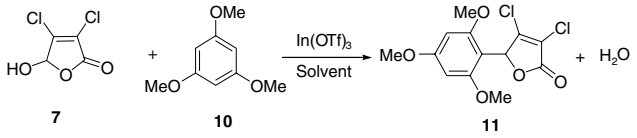
Reaction condition: 20 mL toluene, 24 h, 100–110 °C, water of the reaction not removed. % Conversion is the molar ratio of the product to mucochloric acid as determined by HPLC analysis of the reaction mixture.

[a] Isolated yield and water was removed by the Dean trap.

1,2,3-trimethoxybenzene disappeared indicating it must undergo some side reaction or decomposition due to the stability and reactivity of 1,2,3-trimethoxybenzene **8**. The purple color is possibly from the oxidation of 1,2,3-trimethoxybenzene or a Friedel–Crafts intermediate which gave a benzoquinone-like structure. Thus, we decided to use 1.5 equiv of the electron-rich aromatic compound, 1,3,5-trimethoxybenzene **10** as starting material for further study, which provided sole product **11**.

Although toluene was used initially, CH_3NO_2 and CH_2Cl_2 emerged as the superior solvents (Table 2) for this reaction, giving excellent conversion (entries 1, 7–9) and can be operated under mild reaction conditions. Unfortunately, developing methodology that employed a green solvent was of considerable importance. This prompted further investigation of reaction solvents, and unexpectedly to our delight, when reactions were repeated using standard glassware and in the absence of 4 Å molecular sieves, both EtOAc (entry 12) and CH_3CN (entry 13) gave superb conversion (with no water removal). Since water did not hinder the reaction, we wondered if water could be used as a sole solvent. Indeed when the reaction was run in water for 48 h at 100 °C, it gave excellent conversion! The more notable reaction was that performed in HOAc (entry 15), providing an extremely high reaction rate and the reaction

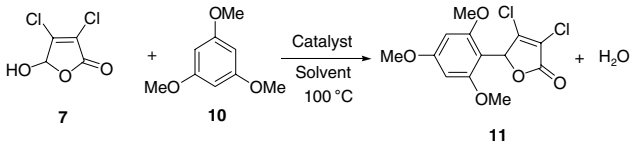
Table 2. Solvent screen in $In(OTf)_3$ catalyzed Friedel–Crafts hydroxyalkylation



Entry	Solvent	Temperature (°C)	Time (h)	Conversion[b] (%)
1[c]	$MeNO_2$	70	15	92
1[e]	$MeNO_2$	100	65	98
2[c]	CH_2Cl_2	40	22	70
3[c]	EtOAc	70	15	28
4[c]	MeCN	70	15	18
5[c]	THF	60	15	6
6[c]	DMF	60	15	0
7	$MeNO_2$	100	2	>99
8	CH_2Cl_2	40	3	95
9	CH_2Cl_2	40	6	>99
10[d]	CH_2Cl_2	40	3	87
11	$CHCl_3$	61	6	99
12	EtOAc	77	6	97
13	MeCN	81	15	98
14	THF	67	23	51
15	H_2O	100	48	98
16	HOAc	100	1	>99

[a] Reaction conditions: 1 equiv (10.0 mmol) of mucochloric acid, 1.5 equiv of 1,3,5-trimethoxybenzene, 0.10 equiv of $In(OTf)_3$ and 20 mL of desired solvent. Water was not removed. Used standard 50 mL rbf and condenser.
[b] Conversion is the molar ratio of the product to mucochloric acid as determined by HPLC analysis of the reaction mixture.
[c] Used carousel reactor tubes and powdered 4 Å molecular sieves were added to the reaction mixtures.
[d] Used 0.10 equiv of $InCl_3$ instead of $In(OTf)_3$.
[e] 10% $In(OAc)_3$ was used.

Table 3. Brönsted acid catalyzed Friedel–Crafts hydroxyalkylation



Entry	Solvent	Catalyst	Time (h)	Conversion[b] (%)	Yield (%)
1	$MeNO_2$	TfOH	1	99	86
2	$MeNO_2$	MSA	4	98	86
3	$MeNO_2$	H_2SO_4	1	99	88
4	$MeNO_2$	*p*-TSA	5	98	84
5	$MeNO_2$	CSA	37	92	—
6	$MeNO_2$	Amberlyst 15	10	93	—
7	$MeNO_2$	HOAc	25	22	—
8	$MeNO_2$	HCl	25	36	—
9	$MeNO_2$	H_3PO_4	25	74	—
10	$MeNO_2$	TFA	41	93	—
11	H_2O	SDS	19	92	85
12	HOAc	—	41	92	84
13[c]	HOAc	H_2SO_4	0.5	99	98
14	HOAc/H_2O	H_2SO_4	6	98	95
15[d]	HOAc	H_2SO_4	3	98	91
16[e]	HOAc	H_2SO_4	2	98	95

[a] Reaction conditions: identical to Table 2, footnote a.
[b] Conversion is the molar ratio of the product to mucochloric acid as determined by HPLC analysis of the reaction mixture.
[c] A 92% yield was obtained when mucobromic acid was used.
[d] Used 0.01 equiv catalyst.
[e] Used 1.10 equiv TMB.

was completed in 1 h! This condition also provided the simplest work-up procedure, as when the reaction mixture was diluted with water, the product was precipitated making separation and isolation simple (Table 2).

The development of metal-free process is important for the pharmaceutical industry because a green or environment friendly process would reduce waste. This coupled with the above success pressed us to consider the use of Brönsted acids to catalyze this reaction. It was found in $MeNO_2$, several Brönsted acids promoted this reaction and provided product in excellent conversion and isolated yield (Table 3). The order of their catalytic activity is H_2SO_4 = TfOH > MSA > *p*-TSA > Amberlyst > CSA > TFA > H_3PO_4 > HCl > HOAc. Thus we decided to use HOAc as the reaction solvent and H_2SO_4, the cheap and highly efficient acid as catalyst. It was found that under these modified conditions (10 mol % H_2SO_4 in AcOH) the reaction was completed in only 0.5 h and the product was isolated in 98% yield. This condition was also suitable for mucobromic acid, where the desired product was isolated in an 82% yield (Fig. 2).

Before Brönsted acid catalyzed Friedel–Crafts hydroxyalkylation was studied, we also examined the generality of the $In(OTf)_3$ catalyzed Friedel–Crafts reaction and the results are listed in Figure 2. The general rule is that the more methoxy (MeO–) groups attached to the aromatic ring, the higher the isolated yield of the corresponding γ-butenolide.

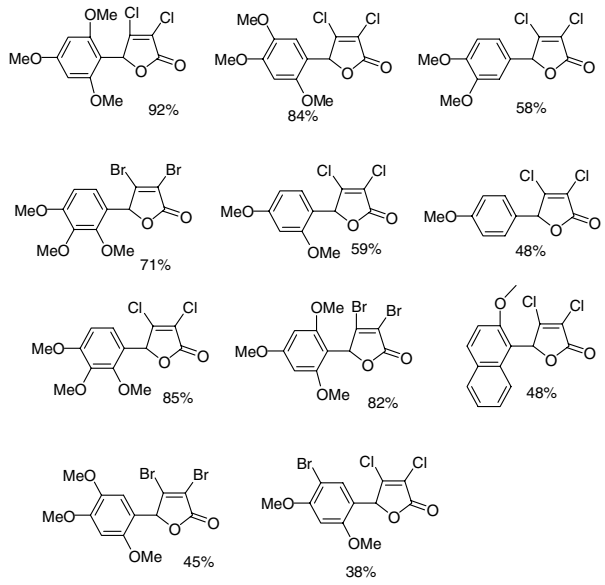
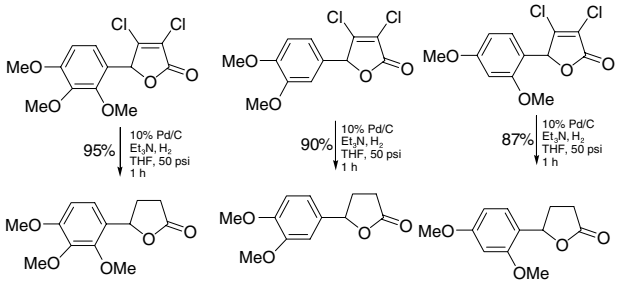


Figure 2. Products from catalytic Friedel–Crafts hydroalkylation of mucohalic acid by using 10 mol % $In(OTf)_3$ in toluene.[19]

The above methodologies have several advantages: (1) both starting materials are inexpensive and commercially available, (2) reactions proceed smoothly, giving moderate to excellent yields, (3) products are functionalized, leading them to further transformations, and (4) a catalytic amount of Lewis acid or Brönsted acid was used (1.5 mol % to 10 mol %). This last point opens a window for using chiral Lewis acids in the asymmetric Friedel–Crafts hydroxyalkylation reactions to prepare optically active γ-butenolides.

With these building blocks in hand, we decided to explore further transformations. The importance of γ-butyrolactones has driven us to access these molecules from these butenolides. A simple, easily operated, clean, and catalytic hydrogenation procedure gave γ-butyrolactones in good to excellent yield (Scheme 2).

In summary, we have developed a simple, efficient, and selective method to prepare a variety of highly functionalized, γ-aryl γ-butenolides using catalytic indium triflate or Brönsted acid in the Friedel–Crafts hydroxyalkylation–lactonization process. Further investigations, including synthesis of novel butenolide-based antioxidants using these synthons via Suzuki coupling will be reported in due course.



Scheme 2. Preparation of γ-butyrolactones via hydrogenation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.009.

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19. All compounds were made by using the initial condition (10 mol % $In(OTf)_3$ in toulene) without optimization or using 10 mol % H_2SO_4 as catalyst.