Selective Synthesis of 2-Aryl-2*H*- and 4-Aryl-4*H*-3,5-diformylpyrans from Acetal with Aromatic Aldehydes Catalyzed by Lewis Acids

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Abstract: A selective method for 2-aryl-2*H*- and 4-aryl-4*H*-3,5-diformylpyrans synthesis from 1,1,3,3-tetramethoxypropane and aromatic aldehydes was developed using an $FeCl_3$ catalyst in MeOH–AcOH and an $AlCl_3$ catalyst in DMA–AcOH.

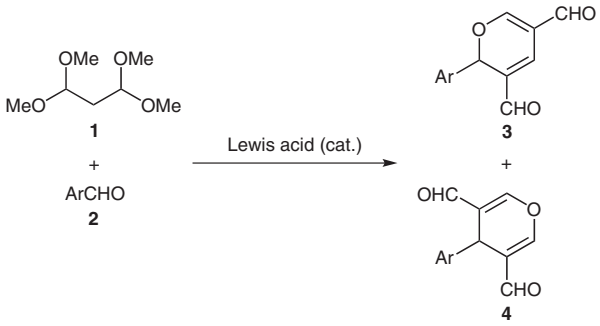
Key words: acetals, pyrans, aldehydes, Lewis acids, catalysis

Pyrans are core structures in biologically active materials and natural products.[1,2] In particular, formylpyran is a key fragment in pharmaceuticals such as antileishmanial drugs.[3] Despite the widespread use of the formyl functionality in synthetic chemistry, a limited number of works on the synthesis of formylpyrans and their derivatives have been reported.[4] Shaabani and co-workers reported the preparation of dialkyl 5-formyl-2*H*-pyran-2,3-dicarboxylates by an intramolecular Wittig reaction.[4a] Perumal and co-workers reported the preparation of 2-imino-2*H*-pyrancarboxaldehydes by the reaction of β-keto amides with a Vilsmeier reagent.[4b]

Although diformylpyrans are potentially far better building blocks in organic synthesis, less attention has been paid to their preparation.[5] For example, 4-phenyl-4*H*-3,5-diformylpyran (**4a**) was prepared by oxidation of cycloheptatrienylmalonaldehyde to benzylidenemalonaldehyde, followed by treatment with malonaldehyde.[5a] However, the existing approach requires a multistep process, and stoichiometric amounts of waste salts are formed in the course of the reaction. The development of a facile and one-step synthetic method for the synthesis of 2*H*- and 4*H*-diformylpyrans, using easily accessible substrates, is therefore a highly desirable and challenging target.

We recently reported that the $FeCl_3 \cdot 6H_2O$-catalyzed cross-cyclodimerization of acetals, such as 3,3-diethoxypropionate with active methylene compounds, leads to coumalates as the major products.[6] During the course of this study, we describe here a novel selective synthetic method for 2-aryl-2*H*-3,5- and 4-aryl-4*H*-3,5-diformylpyrans from 1,1,3,3-tetramethoxypropane and aromatic aldehydes using a Lewis acid catalyst (Scheme 1). This reaction provides a selective method for the synthesis of these diformylpyrans by simply switching the catalyst and the solvent system in easily accessible substrates.

1,1,3,3-Tetramethoxypropane (**1**) with benzaldehyde (**2a**) was chosen as the model substrate, and the reaction was carried out under various conditions (Table 1).



Scheme 1

For example, reaction of **1** (1 mmol) with **2a** (5 mmol) in the presence of $FeCl_3 \cdot 6H_2O$ (0.1 mmol, 20 mol% based on the amount of **1** used) in MeOH–AcOH (1 mL:2 mL) at 50 °C for 15 hours afforded 2-phenyl-2*H*-3,5-diformylpyran (**3a**) in 75% yield along with 4-phenyl-4*H*-3,5-diformylpyran (**4a**) in only 2% yield (Table 1, entry 1). The reaction was highly regioselective and afforded **3a** almost exclusively (the selectivity of **3a** was 97%). The reaction using $FeCl_3$ gave similar results, and **4a** was not detected at all by GC analysis (entry 2). In this reaction, the use of excess amount (5 equiv) of **2a** was effective to achieve the reaction in high yields. Thus, when 1 equivalent (1 mmol) and 3 equivalents (3 mmol) of **2a** were used toward **1**, the yield of **3a** was decreased to 27% and 48%, respectively (entries 3 and 4).

The catalytic activity and the selectivity of this reaction were markedly influenced by the choice of Lewis acid; it was found that $FeCl_3 \cdot 6H_2O$ was the best catalyst for regioselective formation of **3a** (entry 1). Reactions using other selected Lewis acids such as $CeCl_3 \cdot 7H_2O$, $YbCl_3 \cdot 6H_2O$, and $ScCl_3 \cdot 6H_2O$ resulted in a decrease in the yields of **3a** (entries 5–7). The reaction was also affected by the solvent employed, and the best result with regard to selective formation of **3a** was obtained in a mixed solvent of MeOH (1 mL) and AcOH (2 mL). Here, AcOH would play an important role in the efficient generation of 1,3-diformylpropane (**A**, vide infra) by acid-assisted hydrolysis of **1**.[6,7]

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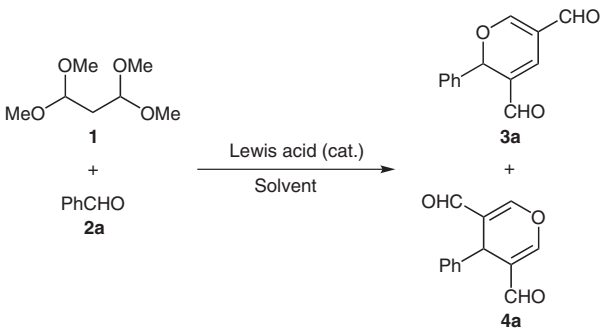
Table 1 Lewis Acid Catalyzed Coupling of 1,1,3,3-Tetramethoxypropane (**1**) with Benzaldehyde (**2a**) under Various Conditions[a]



Entry	Lewis acid	Solvent (mL)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	$FeCl_3·6H_2O$	MeOH (1)–AcOH (2)	75 (69)	2
2	$FeCl_3$	MeOH (1)–AcOH (2)	70	n.d.
3[c]	$FeCl_3·6H_2O$	MeOH (1)–AcOH (2)	27	1
4[d]	$FeCl_3·6H_2O$	MeOH (1)–AcOH (2)	48	2
5	$CeCl_3·7H_2O$	MeOH (1)–AcOH (2)	29	4
6	$YbCl_3·6H_2O$	MeOH (1)–AcOH (2)	33	4
7	$ScCl_3·6H_2O$	MeOH (1)–AcOH (2)	46	4
8	$FeCl_3·6H_2O$	MeOH (3)	n.d.	n.d.
9	$FeCl_3·6H_2O$	AcOH (3)	48	n.d.
10	$AlCl_3·6H_2O$	MeOH (1)–AcOH (2)	8	21
11	$AlCl_3$	MeOH (1)–AcOH (2)	8	29
12	$AlCl_3·6H_2O$	DMA (1)–AcOH (2)	5	52 (43)
13	$AlCl_3·6H_2O$	DMF (1)–AcOH (2)	6	41
14	$AlCl_3·6H_2O$	DMSO (1)–AcOH (2)	12	22
15	$AlCl_3·6H_2O$	DMI (1)–AcOH (2)	19	30
16	$AlCl_3$	DMA (1)–AcOH (2)	2	17
17	$AlCl_3·6H_2O$	DMA (3)	n.d.	2
18	$AlCl_3·6H_2O$	AcOH (3)	3	3
19	$FeCl_3·6H_2O$	DMA (1)–AcOH (2)	10	9

[a] Conditions: **1** (1 mmol) was allowed to react **2a** with (5 mmol) in the presence of Lewis acid (0.1 mmol) in solvent at 50 °C for 15 h.
[b] GC yields based on **1** used. The numbers in parentheses show isolated yields.
[c] Compound **2a** (1 mmol) was used.
[d] Compound **2a** (3 mmol) was used.

Indeed, the reaction in the absence of AcOH did not produce any **3a** (entry 8). In this reaction, the use of MeOH as a cosolvent with AcOH gave a higher yield of **3a** (entry 1 vs. entry 9).

It is noteworthy that changing the Lewis acid not only had a significant impact on the reactivity, but also affected the selectivity between **3a** and **4a**. Thus, the reactivity of the reaction using $AlCl_3·6H_2O$ as the catalyst, under the same conditions as in entry 1, was lower than that of the reaction using $FeCl_3·6H_2O$ as the catalyst (entry 10). In addition, a divergent inverse regiochemistry was apparent and 4-phenyl-4*H*-3,5-diformylpyran (**4a**) was obtained as the major isomer (entry 10).

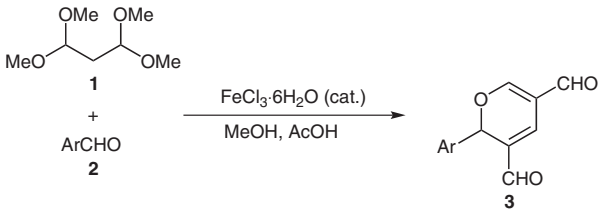
Further screening of the reaction revealed that selection of appropriate solvents enhances the reactivity and selectivity of the $AlCl_3·6H_2O$-catalyzed reaction. The reaction of **1** with **2a** in a mixed solvent of *N*,*N*-dimethylacetamide (DMA) and AcOH (1:2) gave the highest yield and selectivity for **4a** (entry 12). The solvent effect was investigated by examining the reaction in several selected solvents combined with AcOH (entries 12–15). The use of *N*,*N*-dimethylformamide (DMF) gave a comparable result to that obtained with DMA, but other solvents, for example, dimethyl sulfoxide (DMSO) and 1,3-dimethyl-2-imidazolidinone (DMI), gave low yields of **4a** with low regioselectivities (entries 13–15). As mentioned above, the use of AcOH as solvent is crucial to achieve the reaction. For example, in the reaction using only DMA as the solvent, **1** was not completely converted, and the yield of **4a** was only 2% (entry 17). Furthermore, the reaction in the absence of DMA resulted in complete conversion of **1**, but no desired products **3a** and **4a** were obtained (entry 18). These results indicate that both AcOH and a coordinating solvent like DMA are necessary to achieve the $AlCl_3·6H_2O$-catalyzed reaction.

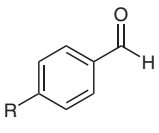
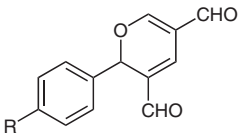
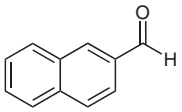
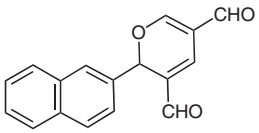
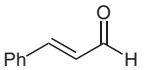
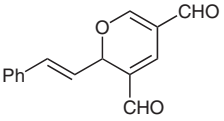
As Lewis acid, protic acid such as *p*-toluenesulfonic acid was ineffective to afford **3a** and **4a** in only 2% and 9% yields, respectively, under the conditions of entry 1.

The substrate scope was then investigated under the optimized conditions for the formation of **3**, using $FeCl_3·6H_2O$ as the catalyst in a MeOH–AcOH solvent system, as shown in Table 1, entry 1. The results are listed in Table 2. The reactions of **1** with a variety of aromatic aldehydes **2a–i** afforded the corresponding 2-aryl-2*H*-3,5-diformylpyrans **3a–i** in moderate to excellent yields with high regioselectivities (Table 2). Among the aldehydes **2** examined in this study, aromatic aldehydes having electron-withdrawing groups gave higher yields of **3** than did aromatic aldehydes having electron-donating groups (entries 1–7). When 2-naphthaldehyde (**2h**) was used, 2-naphthyl-2*H*-3,5-diformylpyran (**3h**) was obtained exclusively, in 78% isolated yield (entry 8). The reaction with *trans*-cinnamaldehyde (**2i**) was sluggish and gave the corresponding diformylpyran (**3i**) in low yield (10%; Table 2, entry 9). The use of aliphatic aldehyde such as 2,2-dimethylpropionaldehyde did not induce diformylpyran derivatives at all.

We then examined the reaction of **1** with **2** using $AlCl_3·6H_2O$ in DMA–AcOH, as shown in Table 1, entry 10. The results are listed in Table 3. Various aromatic aldehydes **2a–i** were reacted with **1** to afford the corresponding 4-aryl-4*H*-3,5-diformylpyrans **4** in moderate to good yields with high regioselectivities (Table 3). The regiochemistry of the products, that is, 2-aryl-2*H*-3,5-di-

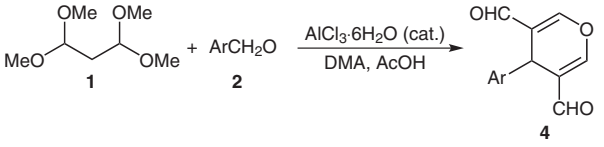
Table 2 $FeCl_3 \cdot 6H_2O$-Catalyzed Synthesis of 2-Aryl-2*H*-3,5-diformylpyrans **3** from **1** and Aromatic Aldehydes **2**[a]

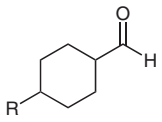
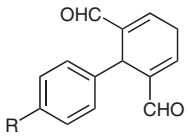
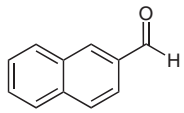
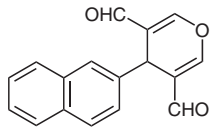
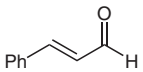
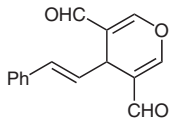


Entry	Aldehyde **2**	Yield of product **3** (%)[b]	Selectivity of **3**/**4**[c]
			
1	**2a** R = H	**3a** 69	38:1
2	**2b** R = Me	**3b** 56	27:1
3	**2c** R = OMe	**3c** 35	15:1
4	**2d** R = Cl	**3d** 62	25:1
5	**2e** R = CN	**3e** 57	12:1
6	**2f** R = CHO	**3f** 65	10:1
7	**2g** R = CF_3	**3g** 85	7:1
8	 **2h**	 **3h** 78	–[d]
9	 **2i**	 **3i** 10	6:1

[a] Conditions: **1** (1 mmol) was allowed to react with **2** (5 mmol) in the presence of $FeCl_3 \cdot 6H_2O$ (0.1 mmol) in MeOH–AcOH (1 mL:2 mL) at 50 °C for 15 h.
[b] Isolated yields of **3** as pure form.
[c] Determined by GC.
[d] Compound **3** was obtained exclusively, and compound **4** was not detected by GC.

Table 3 $AlCl_3 \cdot 6H_2O$-Catalyzed Synthesis of 4-Aryl-4*H*-3,5-diformylpyrans **4** from **1** with Aromatic Aldehydes **2**[a]



Entry	Aldehyde **2**	Yield of product **3** (%)[b]	Selectivity of **3**/**4**[c]
			
1	**2a** R = H	**4a** 43	1:10
2	**2b** R = Me	**4b** 34	–[d]
3	**2c** R = OMe	**4c** 40	1:7
4	**2d** R = Cl	**4d** 60	1:16
5	**2e** R = CN	**4e** 73	1:70
6	**2f** R = CHO	**4f** 66	–[d]
7	**2g** R = CF_3	**4g** 80	1:53
8	 **2h**	 **4h** 51	1:22
9	 **2i**	 **4i** 34	–[d]

[a] Conditions: **1** (1 mmol) was allowed to react with **2** (5 mmol) in the presence of $AlCl_3 \cdot 6H_2O$ (0.1 mmol) in DMA–AcOH (1 mL:2 mL) at 50 °C for 15 h.
[b] Isolated yields of **4** as pure form.
[c] Determined by GC.
[d] Compound **4** was obtained exclusively, and compound **3** was not detected by GC.

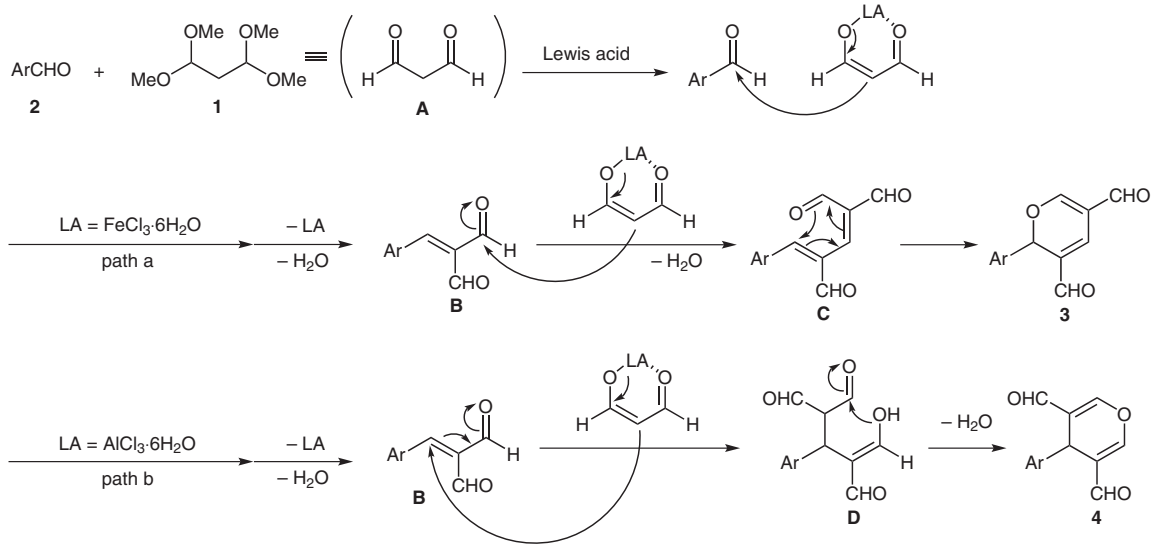
formylpyrans **3** or 4-aryl-4*H*-3,5-diformylpyrans **4**, could therefore be changed by choosing a suitable catalyst/solvent system.

The detailed mechanism of this reaction has not yet been fully confirmed at this moment, but a plausible reaction mechanism for the transformation of **1** with **2** into **3** and **4** is shown in Scheme 2.

The reaction is thought to initiate the acid-assisted hydrolysis of **1** to the intermediate 1,3-diformylpropane (**A**).[6–8] Subsequently, an aldol-type condensation of **A** with **2**, under the influence of a Lewis acid ($FeCl_3 \cdot 6H_2O$ or $AlCl_3 \cdot 6H_2O$), affords the α,β-unsaturated aldehydes **B**.[9]

When $FeCl_3 \cdot 6H_2O$ is used as the catalyst, an enolate generated from **A** reacts with **B** through 1,2-addition to the C=O group of **B** to afford **C**. Intramolecular cyclization then gives **3** as the product (path a, Scheme 2). In contrast, when the reaction is performed with an $AlCl_3 \cdot 6H_2O$ catalyst in AcOH–DMA, the enolate generated from **A** reacts with **B** by 1,4-addition (Michael-type addition), prior to the 1,2-addition to the C=O group, giving the intermediate **D**. Intramolecular cyclization affords **4** as the product (path b, Scheme 2).

Heathcock and co-workers published a detailed discussion of 1,2- vs. 1,4-addition of α,β-unsaturated aldehydes.[10] They reported that α,β-unsaturated aldehydes precede 1,2-addition.[11] In contrast, the alternative Michael-type reaction of α,β-unsaturated aldehydes has conven-



Scheme 2 Plausible reaction mechanism

tionally been performed in protic solvents in the presence of a base, which assisted conversion of the nucleophile to its enolate form.[10,12] The regiochemistry of the α,β-unsaturated aldehydes is influenced by the solvent, the counterion, and the electronic nature of the enolate.[8] The role of DMA is as yet unclear, but a basic solvent such as DMA would accelerate the enol-forming step from **A** in the reaction, which predominates Michael-type addition as shown in path b, Scheme 2.

In conclusion, we reported the synthesis of 2-aryl-2*H*- and 4-aryl-4*H*-3,5-diformylpyrans from 1,1,3,3-tetramethoxypropane with various aromatic aldehydes. The present reaction provides a facile and efficient synthetic method using easily accessible starting materials. Furthermore, the selective formation of 2-aryl-2*H*-3,5-diformylpyrans and 4-aryl-4*H*-3,5-diformylpyrans was achieved simply by tuning the catalyst/solvent system. Further studies of the scope and synthetic applications of the reaction, and a detailed elucidation of the reaction mechanism, are currently being performed.

A Typical Reaction Procedure for the Preparation of Compound 3a (Table 1, Entry 1)

A mixture of $FeCl_3·6H_2O$ (27 mg, 0.1 mmol, 20 mol%), **1** (164 mg, 1 mmol), and **2a** (531 mg, 5 mmol) in MeOH (1 mL) and AcOH (5 mL) was stirred at 50 °C for 15 h under air (1 atm). The conversions and yields of products were estimated from peak areas based on an internal standard using GC, and the product **3a** was obtained in 75% yield. The reaction mixture was neutralized by 5% aq $NaHCO_3$ and was extracted with EtOAc (30 mL). The organic layer was evaporated under reduced pressure to remove unreacted **2a**. The product **3a** was isolated by column chromatography (230–400 mesh silica gel, *n*-hexane–EtOAc = 3:1) in 69% yield (74 mg). White solid (mp 110–112 °C). ^{1}H NMR: δ = 9.59 (s, 1 H, CHO), 9.39 (s, 1 H, CHO), 7.55–7.57 (m, 2 H, CH), 7.39 (s, 5 H, Ph), 6.48 (s, 1 H, CH). ^{13}C NMR: δ = 189.68 (CHO), 185.70 (CHO), 166.80 (OCH), 137.00 (C), 133.20 (CH), 129.87 (CH), 128.96 (CH), 128.42 (C), 127.35 (CH), 117.15 (C), 79.02 (CH). IR (neat): 3033, 2859, 1684, 1641, 1563, 1409, 1306, 1193, 1127, 897, 750, 696 cm^{-1}. GC-MS (EI): *m/z* (%) = 214 (26) [M]$^+$, 186 (100), 129 (66), 128 (38), 115 (20). HRMS (EI): *m/z* calcd for $C_{13}H_{10}O_3$ [M]$^+$ 214.0630; found: 214.0636.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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