

A stable intermediate: a new insight into the mechanism of Lewis acids-promoted formation of acylals from aldehydes

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Abstract—Treatment of *m*-nitrobenzaldehyde with acetic anhydride in the presence of Lewis acids, such as InBr_3 , ZnBr_2 , $\text{Cu}(\text{OTf})_2$, gives a stable intermediate at the initial stage of reaction. Based on this new organic compound characterized by X-ray single crystal diffraction, a new mechanism for Lewis acids-promoted formation of acylals from aldehydes is proposed. Exchange reaction with different ratio of acetic anhydride to propionic anhydride, in the presence of Lewis acids, is studied.

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The development of effective methods for selective protection and deprotection is currently of urgent importance in multistep organic synthesis. The protection of aldehydes as acylals (1,1-diacetates) rather than acetals¹ plays an important role in organic synthesis because of their stability in neutral and basic medium² and easy conversion into parent aldehydes.³ In addition, acylals are useful starting materials and intermediates in organic synthesis.⁴ Generally, 1,1-diacetates can be prepared from aldehydes by treatment with acetic anhydride in the presence of a suitable catalyst such as proton acids, Lewis acids,⁵ heteropolyacids,⁶ solid acids⁷ and so on.⁸ Among these catalysts, Lewis acids enjoy a wide substrate scope, mild conditions, good chemoselectivity and excellent yields.

To the best of our knowledge, however, the mechanism of the reaction catalyzed by Lewis acids between aldehydes and acetic anhydride is still unclear.⁹ Pinnick and co-workers proposed an intermolecular mechanism involving an intermolecular transfer of a second acetate group after initial attack by acetic anhydride in the presence of FeCl_3 .¹⁰ Due to our continued interest in InBr_3 ,¹¹ we have carried out a series of experiments to get further insight into the mechanism for this reaction. To our joy, the reaction of *m*-nitrobenzaldehyde and acetic anhydride in the presence of 1 mol % InBr_3 proceeded and afforded a stable compound **1** at the initial

stage. Surprisingly in the reaction of *m*-nitrobenzaldehyde and acetic anhydride catalyzed by other Lewis acids (X_mY_n), such as ZnBr_2 , $\text{Cu}(\text{OTf})_2$, **1** is also obtained. A small quantity of **1** was separated by flash chromatography¹² and its molecular structure determined by X-ray crystallography (Chart 1). Furthermore, **1** can also react with acetic anhydride to produce 1,1-diacetate in the presence of Lewis acids such as InBr_3 , ZnBr_2 , $\text{Cu}(\text{OTf})_2$. Treatment of two molecules of aldehyde with one molecule of acetic anhydride under the catalysis of a Lewis acid leads to the formation of **1** in a reasonably high yield in ethyl acetate.¹³ In light of this result, we think that **1** is a key intermediate in this

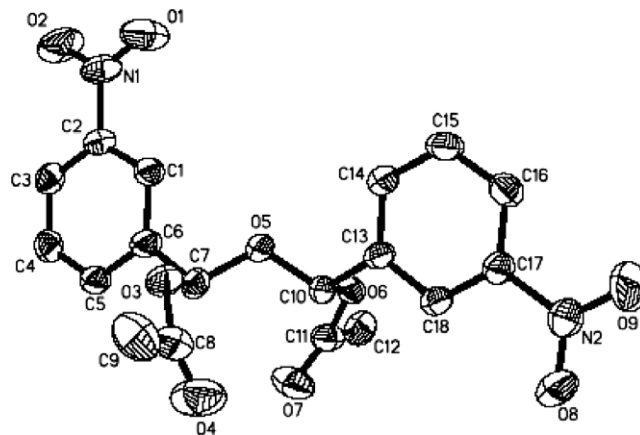
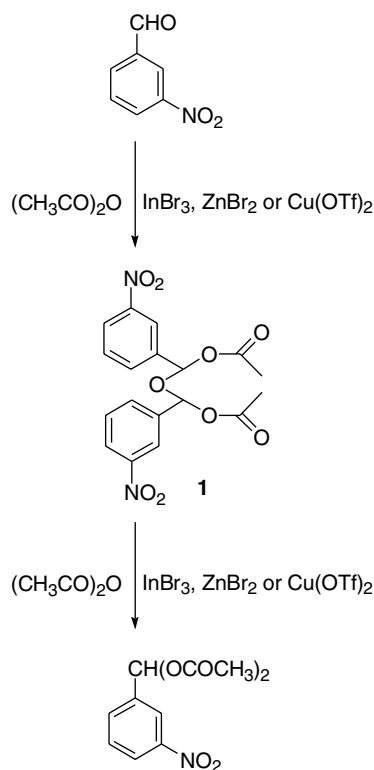


Chart 1. X-ray crystal structure of **1**.

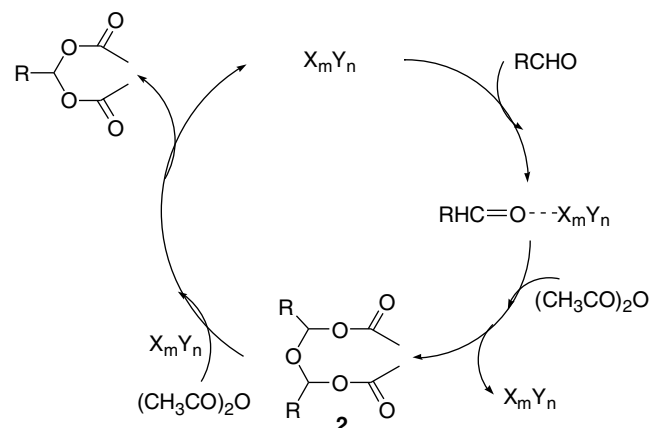
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reaction and the reaction should be divided into two processes. First, two *m*-nitrobenzaldehyde molecules react with one acetic anhydride molecule to give one molecule of **1** in the presence of Lewis acids. Another acetic anhydride activated by Lewis acids then attacks **1** in the following step to afford 1,1-diacetate as the final product (Scheme 1).

Based on the separated intermediate **1**, the mechanism of the formation of acylals is proposed in Scheme 2. With the activation of carbonyl group of aldehyde by coordinating its oxygen to Lewis acids (such as InBr_3 , ZnBr_2 or $\text{Cu}(\text{OTf})_2$), the transformation commences with the reaction between two aldehyde molecules activated by Lewis acids and one acetic anhydride molecule. The dissociation of Lewis acids from the original carbonyl group leads to a stable intermediate **2**. We originally considered that 1,1-diacetate would be obtained by the reaction of **1** and acetic anhydride in the absence of Lewis acids. But GS analysis of a reaction mixture of **1** and acetic anhydride indicates that no 1,1-diacetate is obtained in ethyl acetate while intermediate **1** is quantitatively recovered instead. On the other hand, in the presence of Lewis acids, such as ZnBr_2 , InBr_3 or $\text{Cu}(\text{OTf})_2$, TLC analysis indicates that **1** completely disappeared in ethyl acetate and the corresponding 1,1-diacetate is obtained nearly quantitatively, confirming that Lewis acid is required to facilitate the following process. Subsequent nucleophilic attack on **2** by acetic anhydride activated by Lewis acids and near simultaneous dissociation of Lewis acids from the acetic anhy-



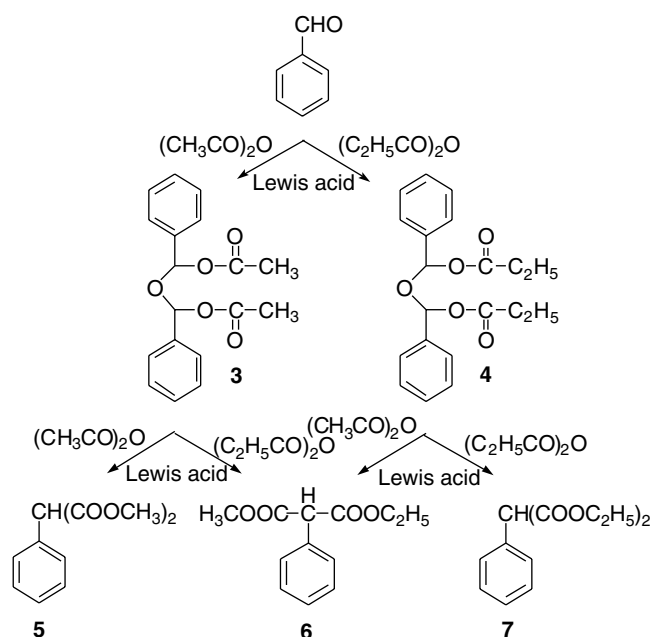
Scheme 1. Conversion of *m*-nitrobenzaldehyde to corresponding 1,1-diacetate in the presence of Lewis acids, such as InBr_3 , ZnBr_2 or $\text{Cu}(\text{OTf})_2$.



Scheme 2. Proposed mechanism of reaction between aldehyde and acetic anhydride in the presence of Lewis acids.

dride generate 1,1-diacetate. Because of the similarities between Lewis acids, it is reasonable to expect that this reaction catalyzed by other Lewis acids will be quite similar to InBr_3 , ZnBr_2 or $\text{Cu}(\text{OTf})_2$ -promoted transformation.

To further verify our proposed mechanism, a variation of the above reaction, in which a mixture of acetic anhydride and propionic anhydride at a ratio of 1:1 is employed instead of acetic anhydride alone, is carried out in the presence of different Lewis acids (Scheme 3).¹⁴ However, **3** and **4** have not been observed in the reactions. When ZnBr_2 , InBr_3 or $\text{Cu}(\text{OTf})_2$ are used as catalysts at a substrate to catalyst ratio of 100:1, geminal diacetate **5**, mixed acetate/propionate **6** and geminal dipropionate **7** are obtained in the ratio 27.0:49.7:23.3, 28.7:49.9:21.3 or 25.3:50.1:24.6, as determined by



Scheme 3. Exchange reaction in the presence of Lewis acids (such as InBr_3 , ZnBr_2 and $\text{Cu}(\text{OTf})_2$).

Table 1. Exchange reaction in the presence of InBr₃^a

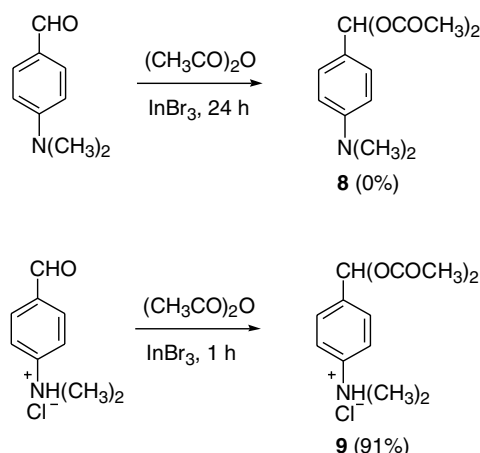
Entry	Ratio ^b	5 (%)	6 (%)	7 (%)
1	10:1	79.7	18.5	1.8
2	5:1	65.9	31.0	3.1
3	2:1	42.6	45.3	12.1
4	1:1	22.4	51.4	26.2
5	1:2	9.9	44.1	46.0
6	1:5	2.8	27.1	70.0
7	1:10	1.2	16.2	82.6

^a Benzaldehyde (10 mmol), acetic anhydride and propionic anhydride (30 mmol), InBr₃ (0.1 mmol).

^b Ratio of acetic anhydride to propionic anhydride.

GC/MS, respectively. Furthermore, the mixtures of acetic anhydride and propionic anhydride at different ratios were also used to react with benzaldehyde in the presence of InBr₃ (Table 1). It is evident that the concentration of **5** and **7** increases with enhancement of ratio of corresponding anhydride to the other. However, with the increasing ratio of one anhydride to the other, the concentration of **6** firstly increases, but then begins to decrease.

It has been reported that many catalysts are not suitable for the preparation of *gem*-diacetates from aromatic aldehydes with an amino group, such as *p*-(dimethylamino) benzaldehyde, possibly due to the strong electron-donating dimethylamino group and the existence of the quinonoid structure with an aldehyde which decrease the reactivity of the aldehyde group.¹⁵ It is worth noting that in the case of its protonated species, such as *N,N*-dimethylammonium benzaldehyde, the reaction progressed smoothly at room temperature to afford an excellent yield of the corresponding *gem*-diacetate **9**, which was isolated as its free amine **8** after hydrogencarbonate workup (Scheme 4). However, we believe that the stronger coordinating ability of an amino group than a carbonyl group hinders the reaction. In spite of the strongly electron-withdrawing nature of the *N,N*-dimethylammonium ion, the reaction works well without interfering of the amino functional group. Lewis acids activate the carbonyl group of aldehyde and then the transformation begins.



Scheme 4. Diacylation of *p*-(*N,N*-dimethylammonium) benzaldehyde in the presence of InBr₃.

In conclusion, a stable intermediate is separated and characterized by X-ray crystallography in the reaction of *m*-nitrobenzaldehyde with acetic anhydride using Lewis acids as catalysts. Based on this finding, a plausible mechanism is reasonably proposed. Exchange reaction, in the presence of Lewis acids, such as ZnBr₂, InBr₃ or Cu(OTf)₂, is studied in detail. In light of the proposed mechanism, the inert nature towards acetic anhydride of aromatic aldehydes with an amino group can be reasonably explained.

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Supplementary data

X-ray single crystal diffraction data for **1** are available. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2007.01.007.

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12. **Separation of 1**: A mixture of *m*-nitroaldehyde (1.511 g, 10 mmol), freshly distilled acetic anhydride (3.063 g, 30 mmol) and ZnBr₂ (0.023 g, 0.1 mmol) was stirred at room temperature. After 2 min, ethyl acetate (100 mL) was added and the mixture was washed successively with 1 mol/L NaOH solution (2 × 20 mL), brine (10 mL) and H₂O (10 mL). The organic layer was separated and dried over Na₂SO₄. Further purification was achieved by column chromatograph on silica to give pure **1** (0.045 g, 1.8%). The crystals of **1** were obtained from a mixture of dichloromethane and hexane. ¹H NMR (300 MHz, CDCl₃, TMS): δ 2.153 (s, 6H), δ 7.250 (s, 2H), δ 7.617 (t, *J* = 7.8 Hz, 2H), δ 7.852 (dd, *J* = 1.2 Hz, 7.8 Hz, 2H), δ 8.282 (dd, *J* = 1.2 Hz, 7.8 Hz, 2H), δ 8.390 (s, 2H). Elemental analysis: C₁₈H₁₆N₂O₉. Calcd: C, 53.47; H, 3.99; N, 6.93. Found: C, 53.52; H, 3.96; N, 7.01. CCDC 255816.
13. **Treatment of two molecules of aldehyde with one molecule of acetic anhydride catalyzed by Lewis acids in a low concentration in ethyl acetate**: A mixture of *m*-nitroaldehyde (0.302 g, 2 mmol), freshly distilled acetic anhydride (0.102 g, 1 mmol) and InBr₃ (0.035 g, 0.1 mmol) was stirred in ethyl acetate (2 mL) at room temperature. After 12 h, evaporation of the solvent under reduced pressure gave mixed products. Further purification was achieved by column chromatograph on silica to give *m*-nitroaldehyde (0.139 g, 0.92 mmol), **1** (0.012 g, 0.03 mmol), acylal (0.223 g, 0.88 mmol).
14. **Typical exchange reaction**: Benzaldehyde (1.060 g, 10 mmol) and ZnBr₂ (0.023 g, 0.1 mmol) were added to a mixture of acetic anhydride (1.021 g, 10 mmol) and propionic anhydride (0.301 g, 10 mmol). The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (100 mL) was added and the mixture was washed successively with 1 mol/L NaOH solution (2 × 20 mL), brine (10 mL) and H₂O (10 mL). The organic layer was separated and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure gave mixed products, whose analysis by GC/MS shows the ratio between **5**, **6** and **7**.
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