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A catalyst-free, facile and efficient approach to cyclic ester: synthesis of $4H$-benzo$[d][1,3]$dioxin-4-ones

Feng Lin, Qiuling Song, Yuyu Gao and Xiuling Cui*

We have developed a green and practical method to construct $4H$-benzo$[d][1,3]$dioxin-4-one and its derivatives, which are important structural units in insecticides, promising spice and intermediates to synthesize multiple-substituted benzene derivatives with great value. The catalyst- and additives-free conditions, commercial and cheap starting materials and short reaction time make this transformation pretty practical and attractive.

Introduction

$4H$-Benzo$[d][1,3]$dioxin-4-one and its derivatives are of great promise for their wide applications in organic and pharmaceutical synthesis as well as agriculture. However, there exist few methodologies to build such a structure so far. In a pioneering work, Mowry and co-workers obtained $4H$-benzo$[d][1,3]$dioxin-4-ones from the condensation of salicylic acids with vinyl acetate catalyzed by mercuric acetate in the presence of sulfuric acid (①, Scheme 1).

To avoid using sulfuric acid or metal magma, more convenient methodologies have been developed. For instance, Patrick and co-workers discovered that the reaction of phenyl salicylate with aldehydes could afford the corresponding cyclic products using 1,4-diazabicyclo [2.2.2]octane (DABCO) as a base in 1996 (②, Scheme 1). Salicylic acids could be converted into $4H$-benzo$[d][1,3]$-dioxin-4-ones by reacting with ketone, catalyzed by N,N-4-dimethylamino-pryidine (DMAP) in the presence of stoichiometric SOCl$_2$ (③, Scheme 1) and in the solution of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (④, Scheme 1). Instead of TFA and trifluoroacetic anhydride, catalytic amount of sulfuric acid (H$_2$SO$_4$) and stoichiometric acetic anhydride could be used to prompt this transformation. Gandelman and co-workers accidentally got the $4H$-benzo$[d][1,3]$dioxin-4-one via irradiation of the mixture of $o$-methylsalicylic acid, 1,3-diiodo-5,5-dimethylhydantoin (Dih) and dichloroethylene for 20h under refluxing (⑤, Scheme 1).

However, some challenges still exit in these procedures, such as the unavailable starting materials, limitation of substrate scope, inevitable side reactions and requirement of strong acids. Therefore, a green, practical and efficient approach for $4H$-benzo$[d][1,3]$dioxin-
Initially, the reaction of salicylic acid (1a) with CH₂Cl₂ was chosen as a model reaction to screen the reaction parameters. K₂PO₄·3H₂O was investigated firstly to screen the reaction temperature and solvent. Only a trace amount of the desired product was observed at 60 °C (Table 1, Entry 1). When temperature was raised to 80 °C, the desired product 2a was achieved in 10% yield (Table 1, Entry 2). The yield could be increased to 99% when the reaction was carried out at 100 °C (Table 1, Entry 3). DMF, as solvent, resulted in the same excellent yield (99%) as well (Table 1, Entry 4). However, no product was observed in 1,4-Dioxane, toluene and THF. (Table 1, Entry 5-7) Other bases, such as K₂HPO₄·3H₂O, KHCO₃, K₂CO₃, Na₂CO₃ and NaHCO₃, Pyridine, Cs₂CO₃, NaOH, KOH, NaOEt disfavoured this transformation (Table 1, Entry 8-17). Without CH₂Cl₂, the reaction did not proceed (Table 1, Entry 18). When carried out in sealed tube with 0.25 mL of CH₂Cl₂, the product was observed in 5% yield. Upgrading the temperature to 125 °C, the reaction provided the product in 92% yield after 15h. Similarly, 2a was obtained in 71% yield when the system was charged with 0.1 mL CH₂Cl₂.

With the optimal reaction conditions in hand, various salicylic acids 1 were screened. The results were summarized in Table 2. Various substituted groups at benzene ring, such as methyl, fluoro, chloro, bromo, methoxy, trifluoromethyl, amino, tert-butyl, were tolerated well under the standard reaction conditions and gave excellent yields (Table 2, Entries 1-13). Based on this series of experiments, substituents at ortho-, meta-, and para-position of the aromatic moiety did not significantly affect the outcome (Table 2, Entries 2-4, Entries 5-6, Entries 7-8, Entries 9-10 and Entries 11-13), specially noticing the high reactivity of 1q, with two bulky tert-butyl groups (Table 2, Entry 17). Meanwhile, both of electron-rich (Table 2, Entries 2-4, Entries 11-13), electron-deficient salicylic acids (Table 2, Entries 5-10, Entry 14 and Entry 16) could give excellent yields. Trifluoromethyl group, a significant group in life science as well as the unprotected amino group could be tolerated in this transformation very well (Table 2, Entry 14 and Entry 15), affording the desirable products in 75% and 90% yields, respectively. Notably, halogen groups could survive well under the standard reaction conditions and no cleavage of the C-halogen bond was observed (Table 1, Entries 5-10). Salicylic acid with two chlorine groups could also furnish the desired product in 70% yield (Table 2, Entry 16). These products with halogen groups could be applied for further functionalization to build useful and more complicated molecules.

The above results inspired us to further demonstrate the application of our developed protocol into coupling of salicylic acids with CHCl₃·CH₃ for synthesis of 2-methyl-substituted 4H-benzo[d][1,3]dioxin-4-ones, as were depicted in Table 2 as well S3 in supporting information for screening reaction condition. 1a could be smoothly transformed into the desired products in 65% yield (Table 2, Entry 18). Either electron-donating groups or electron-
Table 2 Syntheses of the products 2a and 3b

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Entry</th>
<th>1</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>(&gt;99%)</td>
<td>14</td>
<td>1n</td>
<td>2n</td>
<td>(75%)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>(99%)</td>
<td>15</td>
<td>1o</td>
<td>2o</td>
<td>(90%)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>(99%)</td>
<td>16</td>
<td>1p</td>
<td>2p</td>
<td>(70%)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>(98%)</td>
<td>17</td>
<td>1q</td>
<td>2q</td>
<td>(98%)</td>
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<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>(97%)</td>
<td>18</td>
<td>1a</td>
<td>3a</td>
<td>(65%)</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>(89%)</td>
<td>19</td>
<td>1b</td>
<td>3b</td>
<td>(49%)</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>(95%)</td>
<td>20</td>
<td>1c</td>
<td>3c</td>
<td>(53%)</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2h</td>
<td>(96%)</td>
<td>21</td>
<td>1f</td>
<td>3f</td>
<td>(55%)</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2i</td>
<td>(90%)</td>
<td>22</td>
<td>1g</td>
<td>3g</td>
<td>(43%)</td>
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<tr>
<td>10</td>
<td>1j</td>
<td>2j</td>
<td>(92%)</td>
<td>23</td>
<td>1k</td>
<td>3k</td>
<td>(43%)</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>2k</td>
<td>(98%)</td>
<td>24</td>
<td>1l</td>
<td>3m</td>
<td>(51%)</td>
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<tr>
<td>12</td>
<td>1l</td>
<td>2l</td>
<td>(99%)</td>
<td>25</td>
<td>1m</td>
<td>3q</td>
<td>(52%)</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>2m</td>
<td>(95%)</td>
<td></td>
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</table>

<sup>a</sup>Reaction conditions: 1 (0.5 mmol), K<sub>2</sub>PO<sub>4</sub>·3H<sub>2</sub>O (1 mmol), CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL), DMF (1.5 mL), 6h, 100°C.

<sup>b</sup>Reaction conditions: 1 (0.5 mmol), K<sub>2</sub>PO<sub>4</sub>·3H<sub>2</sub>O (1 mmol), CH<sub>2</sub>CHCl<sub>2</sub> (0.6 mL), DMF (1.5 mL), 10h, 130°C.

<sup>c</sup>Isolated yields based on 1.®6h. ®8h.
-withdrawing groups at the aromatic rings of salicylic acids were well tolerated, such as Me, OMe, F, Cl, (CH₃)₃C (Table 2, Entries 19-25). The steric hindrance of substituted groups had slightly effect on the transformation. Ortho-substituted salicylic acids were converted to the desired products in relative lower yields, compared to the ones substituted at meta- or para- position (Table 2, Entries 19 vs 20 and Entries 23 vs 24). Substituted salicylic acid 1q with two tert-butyl groups could provide the desired product in 52% yield (Table 2, Entry 25). Summarily, salicylic acid bearing electron-donating groups (methyl, methoxy) and halogen groups (fluoro, chloro) did not give conspicuous differences in yields, and steric hindrance may have a slight impact on the reaction. The overall yields of CHCl₃-CH₄ are lower than CH₂Cl₂ as a starting material, maybe due to that CHCl₃-CH₄ is more crowded than dichloromethane.

The reaction on a larger scale to demonstrate the practicability of this methodology was successfully performed. Products 2a and 2n could be conveniently obtained on 15 mmol scale in yields similar to those on a small scale (e.g., 2a: 99% vs 98%; 2n: 98% vs 98%, respectively) (See S4-5 in Supporting Information).

4H-Benzol[d][1,3]dioxin-4-ones are versatile building blocks in organic synthesis. After this cyclization protocol was established, we looked forward to applying these cyclic products in further transformations (Scheme 3). For the classical hydrolysis reaction, 2a was treated with stoichiometric 48% aqueous KOH, affording the corresponding salicylic acid in 95% yield. When 2a was treated with 10 mol% K₂CO₃ in MeOH, methyl salicylate 1ab was produced in 96% yield. Furthermore, Itaru Sato and co-workers reported that 5 could be successfully converted to 8. 7-(Bromomethyl)-4H-benzol[d][1,3]dioxin-4-one (5) could be obtained through the reaction of 7-(methyl)-4H-benzol[d][1,3]dioxin-4-one (2e) with N-bromosuccinimide (NBS) in the presence of catalytic amount of benzoyl peroxide (Bz₂O₂). Upon treatment of 2a with 4 equiv of LiAlH₄, a 82% yield of 2-(hydroxymethyl)phenol (6) was provided. 2a could also undergo other transformations. For instance, compound 7, a potential ingredient of insecticides, could be prepared using 2a as the starting material, thus potential to replace its analogues to finish their relative reactions.

Consequently, some controlled experiments were carried out for understanding the reaction mechanism (Scheme 4). If 1 equiv of K₂HPO₄·3H₂O participated in the reaction with CH₂Cl₂, 4 was the major product in 28% yield, as well as 2a in 15% yield (eq (1)). Increasing the amount of K₂HPO₄·3H₂O to 2 equiv, the yield of 2a increased to 29%, while 4 was afforded in only 15%. When 4 reacted with CH₂Cl₂ under standard condition for 6 h, 2a was obtained in 46% yield (eq (2)). Prolonging the reaction time to 12 h, 4 furnished 2a in 71% yield. Surprisingly, 2a could not be detected without CH₂Cl₂, indicating that CH₂Cl₂ might involve in the procedure of intramolecular attack. In addition, 4 was not observed when employing K₂PO₄·3H₂O as base in the course of the reaction.

On the basis of the results obtained, a plausible reaction mechanism was proposed and illustrated in Scheme 5. Initially, dehydration of salicylic acid (1a) formed a salt. Subsequently, A reacted with CH₂Cl₂, providing product 2a directly (Scheme 5).

In conclusion, we have developed a practical and efficient method to construct 4H-benzol[d][1,3]dioxin-4-one and its derivatives, which are important structural units in insecticides, promising spacers and intermediates to synthesize multiple-substituted benzene. The catalyst- and additive-free conditions, commercial and cheap starting materials and short reaction time make this transformation pretty green, practical and attractive. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

Acknowledgement

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Notes and references


Metal-free and additive-free base-mediated formation of $4H$-benzo[\(d\)][1,3]dioxin-4-one and its derivatives from salicylic acids and dichloromethane was developed, using dichloromethane (DCM) and 1,1-dichloroethane (1,1-DCE) as a C1 source.