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boxylate, also converted into 3-aminophthalate derivative.

# IrCl<sub>3</sub> or FeCl<sub>3</sub>-catalyzed convenient synthesis of 3-hydroxyphthalates

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#### ARTICLE INFO

ABSTRACT

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It has been well known that phthalic acid derivatives are important starting materials or building blocks for the syntheses of various dyes,<sup>1</sup> typical resin paints,<sup>2</sup> various pharmaceuticals, and biologically active agents.<sup>3</sup> Therefore, a development of convenient synthetic approach to phthalic acid derivatives has still been the current interest. The conventional syntheses of phthalic acid derivatives have been performed mainly using phthalic acid or phthalic acid anhydride.<sup>4</sup> According to the recent letters, a dimethyl acetylenedicarboxylate (DMAD) (1) is used as the starting compound for the syntheses of phthalates via Diels-Alder reactions<sup>5</sup> or transition-metal catalyzed [2+2+2] cycloaddition reactions.<sup>6</sup> In particular, a two-step synthesis consisting of Diels-Alder reaction of furans with 1 and a subsequent ring-opening reaction by Brønsted acids,<sup>7</sup> Lewis acids,<sup>8</sup> or nucleophiles,<sup>9</sup> could open access to the synthesis of 3-hydroxyphthalate derivatives, which are also attractive as salicylate derivatives (Scheme 1).<sup>10</sup>



Scheme 1. A two-step synthesis of 3-hydroxyphthalate derivatives.

Toward the development of a more efficient and convenient method, only a few one-pot methods, which are important from a green chemical viewpoint, for the synthesis of 3-hydroxyphthaletes have been reported. Brun et al. showed that one-pot reactions of

\* Corresponding author. *E-mail address:* sonoda@chem.osakafu-u.ac.jp (M. Sonoda). phenylfurans were performed by ZnI<sub>2</sub> catalyst to give monohydroxy biaryls.<sup>11</sup> Moreno et al. reported that the use of silica-supported Lewis acid catalysts under microwave irradiation promoted the similar one-pot reactions.<sup>12</sup> Ram et al.<sup>13</sup> and Marque and co-workers<sup>14</sup> showed the one-pot methods under thermal conditions using 3-chlorofurans and 2-amino-5-hydroxymethylfurans, respectively. Herein, we report that IrCl<sub>3</sub>·3H<sub>2</sub>O and FeCl<sub>3</sub> were found to be excellent catalysts for the one-pot reaction to afford 3-hydroxyphthalates.

IrCl<sub>3</sub>·3H<sub>2</sub>O or FeCl<sub>3</sub>-catalyzed convenient synthesis of 3-hydroxyphthalates has been achieved by a Diels-

Alder reaction of furans with dimethyl acetylenedicarboxylate, followed by ring-opening aromatization

reaction of the Diels-Alder adducts, 7-oxabicyclo[2.2.1]hepta-2,5-diene derivatives. In addition,

7-azabicyclo[2.2.1]hepta-2,5-diene derivative, derived from N-Boc-pyrrole and dimethyl acetylenedicar-

To begin with, we have examined a ring-opening aromatization reaction of dimethyl 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3a**), which was derived quantitatively from the Diels–Alder reaction of 2-methylfuran (**2a**) with **1** in toluene,<sup>15</sup> under the similar condition of the Diels–Alder reaction of **2a** in the presence of various Lewis acids (Table 1).

When a 10 mol % of IrCl<sub>3</sub>·3H<sub>2</sub>O was used as a catalyst at the lower temperature, a small amount of dimethyl 3-hydroxy-6-methylphthalate (**4a**) was obtained and the starting materials were recovered (entries 1 and 2). We were pleased to observe that the desired ring-opening aromatization of **3a** proceeded smoothly to afford **4a** in 68% yield at 70 °C (entry 3). Moreover, when FeCl<sub>3</sub> was employed as a catalyst, the reaction proceeded quantitatively (entry 7) though other Lewis acids such as CoCl<sub>2</sub>·6H<sub>2</sub>O, FeCl<sub>3</sub>·6H<sub>2</sub>O, NiCl<sub>2</sub>, PdCl<sub>2</sub>, CuCl<sub>2</sub>, ZnI<sub>2</sub>, and Pd(OAc)<sub>2</sub> had no effect (entries 5, 6, 8, 9, 10, 11, and 14). In the cases of metal triflates such as Cu(OTf)<sub>2</sub> and Zn(OTf)<sub>2</sub>, the product **4a** was obtained in moderate yields (entries 12 and 13). On the basis of these results, next we planned to carry out the one-pot reaction using **1** and **2a** (Table 2).

In the presence of  $IrCl_3 \cdot 3H_2O$  catalyst, the reaction of **2a** with **1** in toluene at 70 °C under air proceeded to give **4a** in 68% yield. It implied that  $IrCl_3 \cdot 3H_2O$  catalyst has an insignificant effect on the first Diels–Alder reaction step. Unfortunately, in the case of FeCl<sub>3</sub> or Cu(OTf)<sub>2</sub> as a catalyst, the lower reactivity was observed than





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# Table 1

Ring-opening aromatization of **3a**<sup>a</sup>



<sup>a</sup> Reaction conditions: **3a** (0.5 mmol), catalyst (0.05 mmol), toluene (1 mL), under air.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

#### Table 2

Synthesis of 3-hydroxyphthalate 4a in one-pot method<sup>a</sup>



<sup>a</sup> Reaction conditions: **2a** (0.6 mmol), **1** (0.5 mmol), IrCl<sub>3</sub>·3H<sub>2</sub>O (0.05 mmol), under air.

<sup>b</sup> Based on **1**.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

that in the case of  $IrCl_3$ · $3H_2O$ . Further optimization of the reaction conditions was examined. The other solvents such as CH<sub>3</sub>CN, THF, CHCl<sub>3</sub>, and 1,2-dichloroethane were unfavorable for this reaction (entries 2, 3, and 4). The yield of **4a** increased to 83% by extension of the reaction time to 48 h (entry 5).

The similar one-pot reactions of various furans (**2a–n**) with **1** were examined and the results are summarized in Table 3. The reaction of furans bearing an electron-donating group, such as methyl, *n*-pentyl, or methoxy group at 2-position, proceeded to give the corresponding 3-hydroxyphthalates in good to excellent yields, respectively (entries 1, 2, and 4). In the case of furfuryl alcohol (**2c**), the latter-half of the reaction did not take place and a Diels–Alder adduct **3c** was formed in 90% yield as a sole product (entry 3).<sup>16</sup> Interestingly, when pure **3c** was used for the ring-opening reaction in the presence of IrCl<sub>3</sub>·3H<sub>2</sub>O in toluene, the reaction proceeded to afford an intramolecular lactonization product **5c** in 65% yield (Scheme 2).<sup>17</sup> 2-Phenylfuran (**2e**), 2-(4-methylphenyl)furan (**2f**), and 2-(4-methoxyphenyl)furan (**2g**) were also applicable for this one-pot reaction to give **4e**, **4f**, and **4g** in good

yields, respectively (entries 5, 6, and 7). In contrast, in the case of 2-arylfurans bearing a strong electron-withdrawing group such as nitro, cyano, or trifluoromethyl group, a significant decrease in the reactivity was observed (entries 8, 9, and 10). We attempted to perform the reaction of pure **3h** in the presence of IrCl<sub>3</sub>·3H<sub>2</sub>O in toluene, however, the desired ring-opening reaction did not proceed at all. The reaction of 2-(4-fluorophenyl)furan (**2k**) proceeded to give the corresponding product **4k** in 97% yield (entry 11). The reaction of methyl 2-furoate (**2l**), bearing an unfavorable substituent as a diene for Diels–Alder reaction, did not take place (entry 12). Unfortunately, in the cases of furan (**2m**) and 2,3-dimethylfuran (**2n**), Diels–Alder adducts **3m** and **3n** were obtained, respectively (entries 13 and 14).

Then, we reviewed the experimental procedure and have found another one-pot method using FeCl<sub>3</sub> instead of IrCl<sub>3</sub>·3H<sub>2</sub>O as a catalyst. After the Diels–Alder reaction of **2h** with **1** in the absence of catalyst at 70 °C for 12 h under nitrogen atmosphere, a 10 mol % of FeCl<sub>3</sub> was added and stirred at 110 °C for 36 h to give the desired product **4h** in 62% yield (entry 2 in Table 4). Using this procedure,

#### Table 3

Synthesis of 3-hydroxyphthalates 4 in one-pot method<sup>a</sup>

	ſ	$\begin{array}{c c} R^1 & CO_2 Me & IrCl_{2} \\ R^1 & + & \\ R^2 & CO_2 Me & 48 \end{array}$	$\begin{bmatrix} 3 \cdot 3H_2O \\ mol\% \end{pmatrix} \rightarrow \begin{bmatrix} e, 70 \circ C \\ B h \end{bmatrix} \begin{bmatrix} R^2 \end{bmatrix} \begin{bmatrix} R^2 \end{bmatrix}$	CO <sub>2</sub> Me CO <sub>2</sub> Me	→ R <sup>2</sup> CO <sub>2</sub> R <sup>1</sup> CO <sub>2</sub>	Me Me		
		2 1		3	4			
Entry	Furans R <sup>1</sup>		R <sup>2</sup>		Yield (%) <sup>b,c</sup>			
				3		4		
1	2a	Me	Н	3a	15	4a	83 (82)	
2	2b	C <sub>5</sub> H <sub>11</sub>	Н	3b	2	4b	98 (85)	
3	2c	CH <sub>2</sub> OH	Н	3c	90	4c	0	
4	2d	OMe	Н	3d	8	4d	92 (82)	
5	2e	Ph	Н	3e	10	4e	90 (90)	
6	2f	$4-Me-C_6H_4$	Н	3f	7	4f	93 (93)	
7	2g	$4-MeO-C_6H_4$	Н	3g	9	4g	90 (89)	
8	2h	$4-NO_2-C_6H_4$	Н	3h	95	4h	Trace	
9	2i	4-CN-C <sub>6</sub> H <sub>4</sub>	Н	3i	74	<b>4i</b>	25 (21)	
10	2j	$4-CF_3-C_6H_4$	Н	3j	35	4j	62 (62)	
11	2k	$4-F-C_6H_4$	Н	3k	2	4k	97 (97)	
12	21	CO <sub>2</sub> Me	Н	31	0	41	0	
13	2m	Н	Н	3m	92	4m	2	
14	2n	Me	Me	3n	98	4n	trace	

<sup>a</sup> Reaction conditions: **2** (0.6 mmol), **1** (0.5 mmol), IrCl<sub>3</sub>·3H<sub>2</sub>O (0.05 mmol), under air.

<sup>b</sup> Based on **1**.

 $^{\rm c}\,$  Determined by  $^1{\rm H}$  NMR. Isolated yield in parentheses.



Scheme 2. Ring-opening aromatization of 3c using IrCl<sub>3</sub>·3H<sub>2</sub>O.

# Table 4

Synthesis of 3-hydroxyphthalates 4 using FeCl<sub>3</sub><sup>a</sup>



 $^{\rm a}$  Reaction conditions: 2 (0.6 mmol), 1 (0.5 mmol), FeCl\_3 (0.05 mmol), under nitrogen atmosphere.

Me

Me

4n

4n

<sup>b</sup> Based on **1**.

5

6<sup>d</sup>

<sup>c</sup> Determined by <sup>1</sup>H NMR. Isolated yield in parentheses.

Me

Me

<sup>d</sup> Under air condition.

2n

2n

**2a**, **2i**, and **2n** also converted into the corresponding products **4a**, **4i**, and **4n** in good yields, respectively (entries 1, 3 and 5), though a formation of **4m** from **2m** did not take place (entry 4). The reaction of **2n** with **1** under air condition resulted in the formation of **4n** in 39% yield (entry 6).



Scheme 3. Synthesis of 3-aminophthalate derivative.

Next we planned to apply the similar method to other fivemembered heteroaromatic compounds such as pyrroles and thiophenes. There are a few report on the ring-opening aromatization reactions of 7-azabicyclo[2.2.1]hepta-2,5-dienes.<sup>8e,18</sup> Very interestingly, however, the desired ring-opening aromatization of a *N*-Boc-7-azabicyclo[2.2.1]hepta-2,5-diene **7**, which was synthesized from the Diels–Alder reaction of *N*-Boc-pyrrole (**6**) with **1** in toluene at 110 °C in 55% yield, was transformed in the presence of a 10 mol % of Pd(OAc)<sub>2</sub> to give a 3-aminophthalate **8** in 75% yield (Scheme 3). In this case, an attempt to perform the one-pot reaction was not successful. The use of other catalysts such as MCl<sub>n</sub> listed in Table 1 resulted in no reaction. On the other hand, thiophenes were found to be unfavorable substrates because of a difficulty of initial Diels–Alder reaction.<sup>19</sup>

In summary, we have developed an efficient method for the synthesis of 3-hydroxyphthalates via Diels–Alder reaction of furans with **1** and the subsequent ring-opening aromatization reaction catalyzed by  $IrCl_3 \cdot 3H_2O$  in one-pot method. Further studies of these reactions are now in progress.

### Supplementary data

89 (83)

39 (32)

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.068.

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