## A One-pot Preparation of 1,3-Diarylisobenzofuran

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A simple, practical, and efficient method for one-pot synthesis of symmetric and unsymmetrical 1,3-diarylisobenzofurans has been developed by sequential reactions of methyl 2-formylbenzoate with two identical or different aryl metal species.

Isobenzofuran is  $10\pi$  electron system with a quinoid structure, which makes them a useful intermediate for natural and unnatural product syntheses.<sup>1,2</sup> Among various possibilities, [4 + 2] cycloaddition with dienophiles is a reliable method for the rapid construction of polycyclic structure.<sup>3</sup>

We report herein an efficient access to functionalized 1,3-diarylisobenzofurans<sup>4</sup> via sequential nucleophilic addition to 2-formylbenzoate (Scheme 1). The first nucleophilic addition of aryl anion to formylbenzoate I is a key step for selective generation of adduct II (step 1), which, in turn, undergoes an intramolecular transesterification to give phthalide III (step 2). Second nucleophile addition to III (step 3) and subsequent acid treatment efficiently gives symmetric and unsymmetrical diarylisobenzofuran V (step 4).

Scheme 2 shows the model study for the first nucleophilic addition to 2-formylbenzoate. Upon treatment of methyl 2-formylbenzoate (1a) with 1.1 equiv of PhMgBr ( $-40 \rightarrow 0^{\circ}$ C), the nucleophile selectively attacked the formyl group in 1a. Subsequent transesterification of the resulting adduct A gave 3-phenylphthalide (2a) in 86% yield.<sup>5</sup> Importantly, the choice of aryl metal species is crucial. Use of PhLi gave 2a only in 12% yield, accompanied by a sizable amount of complex mixture of products.

The next step is a second nucleophilic addition to phenylphthalide **2a**. Upon treatment of **2a** with PhMgBr ( $-40 \rightarrow 0$  °C), nucleophilic addition occurred cleanly and subsequent acid treatment gave 1,3-diphenylisobenzofuran (**3a**) in 94% yield (Scheme 3).<sup>6,7</sup> Having a good results in hand, we then attempted to perform all the steps in *one pot*,<sup>8–10</sup> starting from the selective nucleophilic addition to formylbenzoate (Scheme 3). When **1a** was treated with PhMgBr (1.1 equiv), and the TLC assay confirmed the lactone formation, the second nucleophile (1.2 equiv) was added to the reaction mixture, and subsequent acid treatment (CF<sub>3</sub>CO<sub>2</sub>H, r.t.) gave isobenzofuran **3a** in 85% yield. Further experiments revealed that addition of 2.3 equiv of PhMgBr at one time gave similar result (**3a**: 85%).

This one-pot reaction was applicable for various aryl Grignard reagents (Table 1). Typical experimental procedure is represented by double nucleophilic addition with (4-methoxy-phenyl)magnesium bromide (Entry 1): To a solution of 2-formylbenzoate **1a** in THF was slowly added (4-methoxyphenyl)magnesium bromide (2.2 equiv in THF) at -40 °C. After warming to 0 °C, CF<sub>3</sub>CO<sub>2</sub>H (5.2 equiv) was added to the



Scheme 1.



Scheme 2.



## Scheme 3.

reaction mixture. Extractive workup followed by purification by silica gel column chromatography gave diarylisobenzofuran **3b** in 77% yield (Entry 1).<sup>11,12</sup> Similarly, treatment of **1a** with (2-methoxyphenyl)magnesium bromide gave isomeric isobenzofuran **3c** in 77% yield (Entry 2). Aryl Grignard reagent having the electron-deficient fluoro group at the *para*-position is also applicable for the reaction, affording diarylisobenzofuran **3d** (Entry 3). Moreover, dithienyl groups were cleanly introduced, affording 84% yield of 1,3-dithienylisobenzofuran (**3e**), which is attractive as a building block for oligomeric and  $\pi$ -conjugated molecules (Entry 4).<sup>13</sup> Reaction of electron-donating substrate **1b** with two kinds of aryl Grignard reagents also gave the corresponding diarylisobenzofuran **3f** and **3g** in good yields, respectively (Entries 5 and 6).

Moreover, two *different* benzene rings could be introduced *in one-pot* by using two different aryl metal species (Table 2).

When phthalide **2a**, selectively obtained by treatment of **1a** with PhMgBr (1.1 equiv in THF,  $-40 \rightarrow 0$  °C), was treated with (4-fluorophenyl)magnesium bromide (1.3 equiv in THF,  $-40 \rightarrow 0$  °C), unsymmetrical diarylisobenzofuran **4a** was obtained in 75% yield after acidic workup (Entry 1). In a similar manner, the successive nucleophilic addition with phenylmagnesium bro-

	$\frac{1}{1} \xrightarrow{\text{CO}_2\text{Me}}{\text{CHO}} \frac{\text{Ark}}{-40}$	$\frac{\text{MgBr}}{\text{$\to 0 ^{\circ}C$}} \xrightarrow{\text{CF}_3\text{CO}_2\text{F}} 0 ^{\circ}\text{C} \rightarrow \text{r.t}$		Ar O Ar
Entry	Formylbenzoate	Ar	Product	Yield/%
1 <sup>a</sup>	CO <sub>2</sub> Me CHO	-{	3b	77
2 <sup>a</sup>		-ξ- MeO	3c	77
3 <sup>a</sup>		-§F	3d	82
4 <sup>a</sup>		. S	3e	84
5 <sup>a</sup>	MeO MeO 1b CO <sub>2</sub> Me CHO		3f	72
6 <sup>a</sup>		-{	3g	70

 
 Table 1. One-pot preparation of symmetric 1,3-diarylisobenzofuran

<sup>a</sup>2.2-2.4 equiv of ArMgBr.

mide and (2-methoxyphenyl)magnesium bromide gave isobenzofuran **4b** in 68% yield (Entry 2). The dual reactions in the combination with electron-donating and/or electron-deficient nucleophiles gave the corresponding products **4c**–**4e**, respectively (Entries 3–5). In these cases, however, the reaction of **2a** with (4-cyanophenyl)magnesium bromide and 2-pyridylmagnesium bromide gave poor results, only giving the complex mixture of products. Reinvestigation of the reaction conditions revealed that the use of the corresponding aryllithium cleanly gave the desired products **4d** and **4e**, respectively (Entries 4 and 5).<sup>14</sup> The successive processes also proved to be applicable to the combination of (2-thienyl)magnesium bromide and 2-furyllithium, giving **4f**, which could serve as a synthetic intermediate for further elaboration to polyaromatic systems (Entry 6).<sup>13</sup>

For exploring further scope of the one-pot process, we addressed the applicability for the divergent syntheses of isomeric isobenzofuran from a single starting material (Scheme 4). Thus, the treatment of methyl 5-bromo-2-formyl-benzoate (5)<sup>15</sup> with (4-fluorophenyl)magnesium bromide followed by (4-methoxyphenyl)magnesium bromide gave **6** in 61% yield. The *isomeric product* **7** was accessible from the same benzoate **5** in good yield by treating two nucleophiles at opposite turn.

The last but not the least point to note is that structurally attractive bis(isobenzofurans), where two furan moieties are

 
 Table 2. One-pot preparation of unymmetrical 1,3-diarylisobenzofuran

la	,CO₂Me `CHO	$Ar^{1}MgBr$ -40 $\rightarrow$ 0 °C	$ \begin{array}{c} \text{Ar}^{2}\text{Li or} \\ \text{Ar}^{2}\text{MgBr} \\ \hline -40 \rightarrow 0 \ ^{\circ}\text{C} \end{array} $	$\frac{CF_3CO_2H}{0 \text{ °C} \rightarrow r.t.}$	$Ar^2$ 0 $4$ $Ar^1$
Entry	Ar	1	Ar <sup>2</sup>	Product	Yield/%
1 <sup>a</sup>	<u></u>		- <del>§</del> - <b>F</b>	4a	75
2 <sup>a</sup>	-¥-{		·ŧ-	4b	68
3 <sup>a</sup>		F	-§OMe	4c	67
4 <sup>b</sup>	.ş_		-§CN	4d	65
5 <sup>b,c</sup>	<u>.</u>			4e	47
6 <sup>b</sup>	-	s	-se _0	4f	51

 ${}^{a}Ar^{2}MgBr$  was used as a second nucleophile.  ${}^{b}Ar^{2}Li$  was used as a second nucleophile.  ${}^{c}Second$  nucleophile was added at -78 °C.



Scheme 4.

connected by aromatic rings, was accessible in one-pot under the suitable conditions. Indeed, bis(isobenzofuran)  $\mathbf{8}$ , connected by 4,4'-biphenyl, was obtained from 2-formylbenzoate  $\mathbf{1a}$  in good yield by nucleophilic addition of Grignard reagent  $\mathbf{B}$  to  $\mathbf{1a}$ ,





transesterification, bis-addition of 4,4'-dilithiobiphenyl to the intermediate of the phthalide (structure not shown), and dehydration under acidic conditions (Scheme 5).<sup>16</sup>

In summary, we developed a simple, practical, and efficient method for one-pot synthesis of symmetric and unsymmetrical 1,3-diarylisobenzofurans by sequential reactions of methyl 2formylbenzoate with two identical or different aryl metal species. Further studies are currently in progress.

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