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### Titanium Tetrachloride Promoted Cyclodehydration of Aryloxyketones: Facile Synthesis of Benzofurans and Naphthofurans with High Regioselectivity

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## Titanium Tetrachloride Promoted Cyclodehydration of Aryloxyketones: Facile Synthesis of Benzofurans and Naphthofurans with High Regioselectivity

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### ABSTRACT

An efficient and facile method for the synthesis of a broad series of benzofurans and naphthofurans is described. The direct intramolecular cyclodehydration of aryloxyketones in the presence of titanium tetrachloride affords the corresponding benzofurans and naphthofurans with good regioselectivity and yields.

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The arene ring-fused furan core is a ubiquitous heterocyclic motif which has been extensively studied due to its widespread occurrence in natural products, pharmaceuticals, and functional materials.<sup>1</sup> Compounds featuring a benzofuran skeleton have exhibited prominent pharmacological activities, and more than thirty drugs containing benzofuran moieties have been approved by the USFDA.<sup>2</sup> Furthermore, naphthofurans have attracted significant attention in recent years in the development of potential drugs for anticancer,<sup>3</sup> dual inhibitors of Alzheimer's disease,<sup>4</sup> inhibitors of human protein kinase,<sup>5</sup> and regulators of the nuclear receptor,<sup>6</sup> as well as other activities.<sup>7</sup> Several representative bioactive compounds possessing a naphthofuran or benzofuran skeleton are listed in Figure 1.

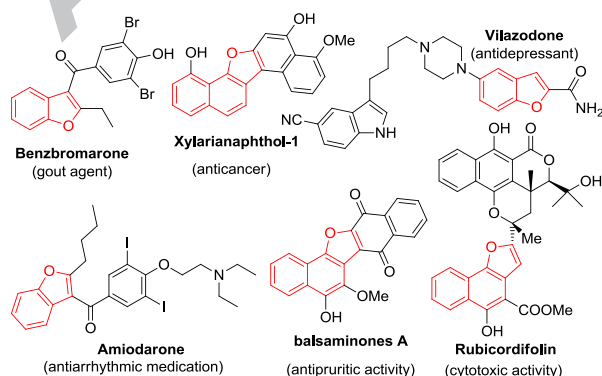


Figure 1. Representative drugs containing benzofuran or naphthofuran cores.

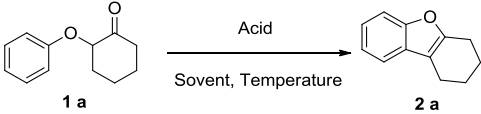
As a consequence, significant attention has been paid to the development of efficient approaches towards these scaffolds.<sup>8</sup> One of them is the intramolecular cyclodehydration reaction of aryloxyketones which can be easily prepared from phenols and  $\alpha$ -haloketones.<sup>9</sup> However, the reported methods for the cyclodehydration of aryloxyketones are limited in their substrate scope and require harsh reaction conditions.<sup>10</sup> Therefore, a milder and more practical cyclodehydration procedure is still in demand.

Titanium tetrachloride is well known as both a powerful dehydrating agent<sup>11</sup> and a strong Lewis acid, which has been applied in various functional group transformations.<sup>12</sup> Recently, we reported an efficient Paal-Knorr furan synthesis using titanium tetrachloride.<sup>13</sup> To further expand its scope, we attempted to carry out the intramolecular cyclodehydration reaction of aryloxyketones employing titanium tetrachloride as a dehydrating agent, which has not been disclosed in the literature.

Firstly, aryloxyketone **1a** was selected as a model substrate to give the desired benzofuran **2a**. The cyclodehydration reaction proceeded smoothly in the presence of most of the Brønsted or Lewis acids (Table 1, entries 1-7). However, the yields were moderate and a prolonged reaction time or a higher reaction temperature was necessary. To our delight, the reaction proceeded quickly when titanium tetrachloride was used (Entry 8). Moreover, it was discovered that increasing or decreasing the amount of titanium tetrachloride led to diminished reaction efficiency (Entries 9-11). A higher reaction temperature was beneficial to the reaction rate rather than the reaction efficiency (Entry 12). The reaction could also be carried out in several conventional solvents (ACN and TFE) in addition to  $\text{CH}_2\text{Cl}_2$ , although resulting in significantly lower conversions and longer

reaction times (Entries 15-16). Using toluene, a high temperature was necessary since almost no conversion was observed when the reaction mixture was stirred at room temperature (Entry 17). Other solvents (THF and DMF) were also screened, but the desired product was not detected after stirring overnight (Entries 13-14).

**Table 1.** Model reaction optimization.

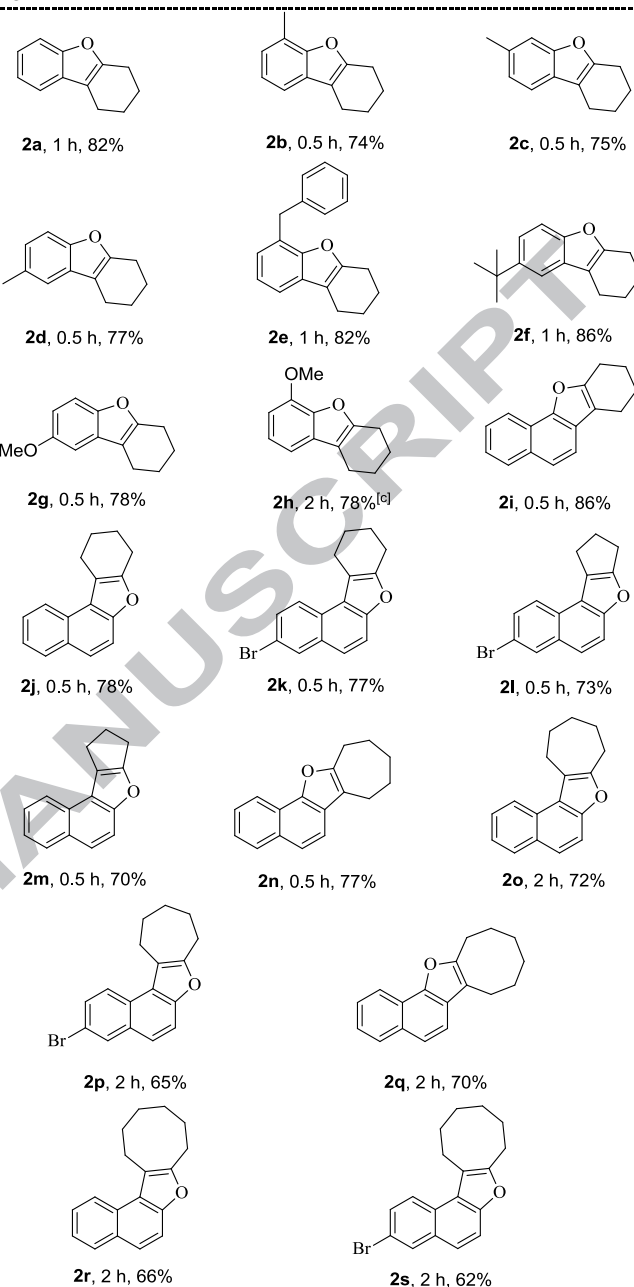
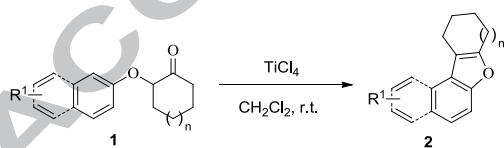


Entry	Acid	Solvent	T [°C]	Time	Yield <b>2a</b> <sup>a</sup>
1	<i>conc.</i> HCl	<sup>b</sup>	reflux	24 h	NA
2	H <sub>2</sub> SO <sub>4</sub> /H <sub>3</sub> PO <sub>4</sub>	<sup>b</sup>	25	1 h	61%
3	CF <sub>3</sub> COOH	CH <sub>2</sub> Cl <sub>2</sub>	25	12 h	49%
4	TsOH	Toluene	reflux	1 h	67%
5	ZnCl <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	25	12 h	49%
6	AlCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	25	12 h	60%
7	Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	reflux	24	NA
8	TiCl <sub>4</sub> (1.0 eq.)	CH <sub>2</sub> Cl <sub>2</sub>	25	1 h	82%
9	TiCl <sub>4</sub> (0.2 eq.)	CH <sub>2</sub> Cl <sub>2</sub>	25	1 h	55%
10	TiCl <sub>4</sub> (0.5 eq.)	CH <sub>2</sub> Cl <sub>2</sub>	25	1 h	69%
11	TiCl <sub>4</sub> (1.5 eq.)	CH <sub>2</sub> Cl <sub>2</sub>	25	1 h	73%
12	TiCl <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	reflux	0.5 h	74%
13	TiCl <sub>4</sub>	THF	25	24 h	NA
14	TiCl <sub>4</sub>	DMF	25	24 h	NA
15	TiCl <sub>4</sub>	ACN	25	4 h	51%
16	TiCl <sub>4</sub>	TFE	25	2 h	62%
17	TiCl <sub>4</sub>	Toluene	reflux	0.5 h	80%

<sup>a</sup>Isolated yield. <sup>b</sup>Without solvent.

Various phenoxycycloketones were then subjected to the titanium tetrachloride mediated condensation reaction (Table 2, **2a–h**). Substrates with an electron-donating group on the benzene ring, such as methyl, methoxy, benzyl, and *tert*-butyl groups, and phenoxycycloketone with an unsubstituted benzene ring all easily undergo cyclodehydration to produce the corresponding benzofuran products in satisfactory yields. In the cases of phenoxycycloketone with a methyl group, the location of the substituted position (*ortho*-, *meta*- and *para*-) on the benzene ring showed no observable effects on the reaction outcomes (Table 2, **2b–d**).

**Table 2.** Condensation reaction of cyclic aryloxyketones.<sup>a, b</sup>



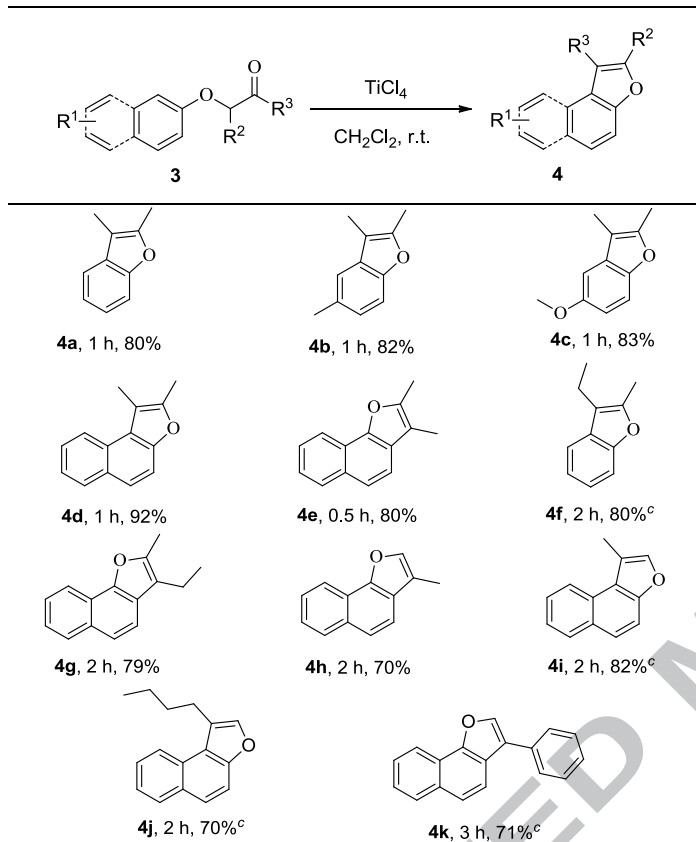
<sup>a</sup> Reagents and conditions: **1** (0.5 mmol), TiCl<sub>4</sub> (0.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), r.t. <sup>b</sup> Isolated yield. <sup>c</sup> 40 °C.

Products **2e** and **2f** also indicated that increased steric hindrance on the benzenoid part of the substrates is tolerated. Interestingly, for the case in which two regioisomers are possible (**2c**), the *meta*-substituted phenoxycycloketone afforded a single isomer with complete regioselectivity. Surprisingly, phenoxycycloketones with a methoxyl group at either the *ortho*- or *para*-position of the phenyl ring exhibited different reactivities. The phenoxycycloketone with an *ortho*-substituted methoxyl group (**2h**) required a higher reaction temperature and longer reaction time compared to phenoxycycloketone (**2g**).

With our preliminary studies complete, we then attempted to extend the reaction scope with different naphthol moieties. To our delight, a variety of cyclic aryloxyketones derived from  $\alpha$ - and  $\beta$ -naphthols functioned efficiently in this transformation (Table 2, **2i–s**). The condensation reactions of aryloxyketones containing five-, six-, seven-, or eight-membered rings were completed in 0.5–2 h at room temperature to give the corresponding tetracyclic furans with good to excellent yields

and complete regioselectivity. Additionally, cyclic aryloxyketones with a bromo group were also suitable substrates. Notably, the cyclodehydration of these unsymmetrical cyclic aryloxyketones occurred preferentially at the 1- or 2-position of the naphthyl moiety, producing the corresponding single isomers.

**Table 3.** Condensation reaction of acyclic aryloxyketones.<sup>a, b</sup>



<sup>a</sup> Reagents and conditions: **1** (0.5 mmol),  $\text{TiCl}_4$  (0.5 mmol),  $\text{CH}_2\text{Cl}_2$  (1 mL), r.t. <sup>b</sup> Isolated yield. <sup>c</sup> 40 °C.

To further demonstrate the utility of this method, several aryloxyketones prepared from acyclic haloketones and phenols were examined. The reactions of aryloxybutanones (Table 3, **4a-e**) proceeded to completion in 1 h at room temperature to give the corresponding benzofurans or naphthofurans with excellent yields. In contrast, the reactions of aryloxy-pentanones (Table 3, **4f-g**) were slower, especially phenoxypentanone (**4f**) which required heating. Moreover, the use of aryloxyketones derived from 1-halo-2-ketones (Table 3, **4h-k**) gave naphthofurans in good to excellent yields. However, the reactions were more sluggish, and longer reaction times and heating were necessary. Remarkably, all unsymmetrical aryloxyketones afforded a single isomer.

In summary, we have developed an efficient method for the synthesis of a diverse range of benzofurans and naphthofurans via the intramolecular cyclodehydration of aryloxyketones using titanium tetrachloride as the dehydrating agent. Cyclic and acyclic aryloxyketones were readily condensed to give the corresponding benzofurans and naphthofurans in good to excellent yields with high regioselectivity.

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## Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

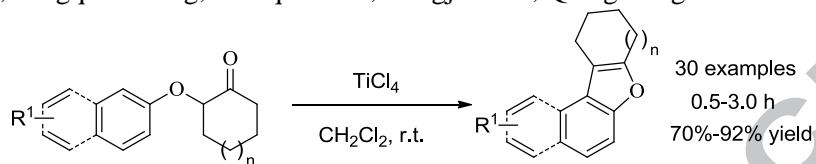
**Graphical Abstract**

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- First utilization of titanium tetrachloride in the intramolecular cyclodehydration of aryloxyketones.
- The cyclodehydration of aryloxyketones with high reaction rates.
- Regioselective synthesis of Benzofurans and Naphthofurans.

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