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Tetrahedron

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# Access to fused pyrroles via the reaction of spiro-dienyl ethers with amines involving a chemoselective skeletal rearrangement

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## ARTICLE INFO

### Article history:

Received 6 March 2014

Received in revised form 20 May 2014

Accepted 22 May 2014

Available online xxx

### Keywords:

Fused pyrroles

Spiro-dienyl ethers

Furan derivatives

Skeletal rearrangement

## ABSTRACT

Under metal-free conditions, the reaction of spiro-dienyl ethers, derived from furan derivatives, with aromatic amines provided fused pyrroles. The reaction proceeded through an interesting and chemoselective skeletal rearrangement and provided an alternative protocol for the construction of pyrrole rings from furan derivatives.

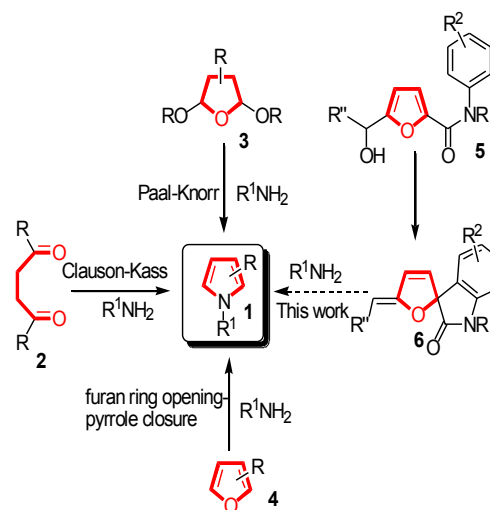
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## 1. Introduction

Pyrrole derivatives **1** are prevalent in a wide variety of biologically and medicinally important compounds<sup>1</sup> and used as building blocks for the construction of pharmaceutical agents<sup>2</sup> and electronic materials.<sup>3</sup> Consequently, numerous methods for their synthesis have been developed over the years, including the Knorr reaction,<sup>4</sup> Hantzsch reaction,<sup>5</sup> Clauson-Kass reaction,<sup>6</sup> Paal–Knorr reaction,<sup>4c,7</sup> transition-metal-mediated reaction,<sup>8</sup> and other operations.<sup>9</sup> Among these methods, the Paal–Knorr and Clauson-Kass reactions are the most commonly used, albeit multi-step synthetic operations are required. A similar protocol based on the furan ring opening–pyrrole closure strategy is also extensively used (Scheme 1).<sup>10</sup> Due to the fact that furan derivatives have attracted great attentions as green, renewable building blocks in organic synthesis,<sup>11</sup> it is highly desirable to develop access to structurally novel pyrroles starting from furan derivatives.

## 2. Results and discussion

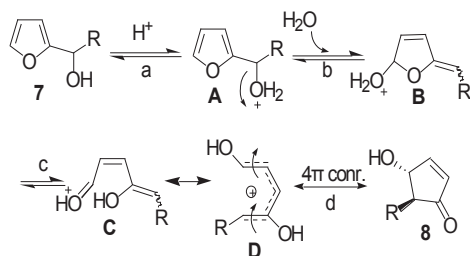
Acid-catalyzed rearrangement of suitable 2-furylcarbinols **7** into 4-hydroxycyclopentenone derivatives **8** (namely Piancatelli rearrangement)<sup>12</sup> has been well used as a key step in the construction of a series of natural products and biologically relevant cyclopentenones.<sup>13</sup> The overall transformation is considered to



Scheme 1. Strategy to synthesize pyrroles from furan or its derivatives.

proceed through a cascade sequence that terminates with a  $4\pi$ -electrocyclic ring closure of a pentadienyl cation (Scheme 2). Recently we and other groups explored the Piancatelli rearrangement in an intramolecular fashion and developed an access to spiro-compounds.<sup>14</sup> More recently, we disclosed an approach to a class of spiro-dienyl ethers **6** from 2-furylcarbinol **5** and explored

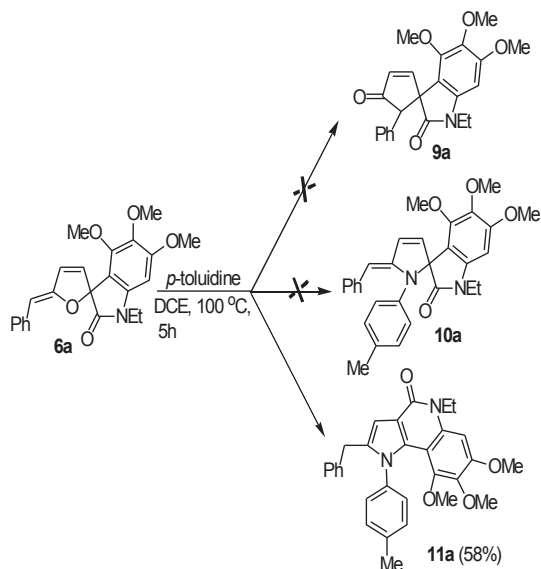
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**Scheme 2.** Proposed mechanism of the Piancatelli reaction. conr.=conrotatory.

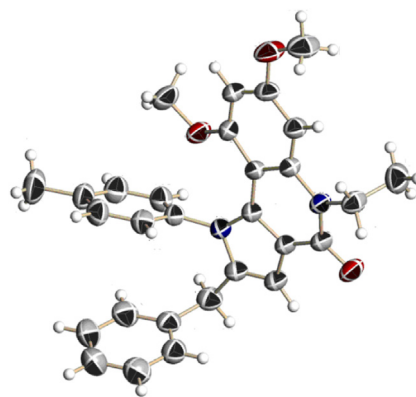
the thermal rearrangement of **6** into cyclopentenone.<sup>15</sup> Given that the highly strained **6** is readily synthesized from furans and it contains multiple reactive sites, it is anticipated that further modification of the spiro-dienyl enol segment of **6** would provide access to a variety of structurally novel heterocycles and thus expand the synthetic application of sustainable material from furan derivatives.

Owing to the importance of spirooxindoles **10a** bearing a 2,5-dihydro-pyrrole subunit in medicinal significance, we attempted to synthesize **10a** via the reaction of **6a** in the presence of *p*-toluidine, assuming that the thermal rearrangement of **6a** into **9a** could be suppressed. However, upon heating **6a** with 4-methylaniline in DCE at 100 °C for 5 h, no expected spirooxindoles **10a** was produced. Instead, a fused pyrrole **11a** was formed in 58% yield (Scheme 3). The structure of **11a** was unambiguously determined by X-ray crystallography (Fig. 1).<sup>16</sup> This unexpected result nonetheless provided an unprecedented access to fused pyrroles with structural novelty from dienyl ether. The reaction of dienyl ether with nucleophiles, such as amine, has never been reported. Exploring such a reaction would expand the synthetic applications of furan derivatives.



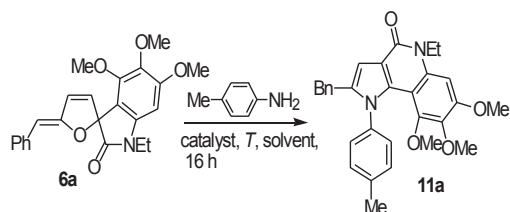
**Scheme 3.** The reaction of **6a** with *p*-toluidine.

We then screened a variety of catalysts, solvents, and reaction temperatures to optimize the reaction as shown in Table 1. The reaction outcome was greatly influenced by the temperature. For instance, lowering the reaction temperature to 80 °C shut down the reaction completely (entry 2). In contrast, a slight increase of temperature to 105 °C enhanced the yield to 65% (entry 3). Further



**Fig. 1.** X-ray crystal structure of compound **11a**.

**Table 1**  
Optimization of the reaction conditions<sup>a</sup>



Entry	Catalyst	T (°C)	Solvent	Yield (%) <sup>b</sup>
1	—	100	DCE	58
2	—	80	DCE	0
3	—	105	DCE	65
4	—	110	DCE	50
5	—	130	DCE	15
6	—	105	Toluene	ND
7	—	105	DMF	ND
8	—	105	Dioxane	54
9	—	105	THF	59
10	CSA	105	DCE	66
11	ZnCl <sub>2</sub>	105	DCE	75
<b>12</b>	<b><i>p</i>-TsOH</b>	<b>105</b>	<b>DCE</b>	<b>84</b>
13	MS 4 Å	105	DCE	80

Bold values signify optimized reaction conditions.

<sup>a</sup> All reactions were performed on a 0.3 mmol scale. Unless otherwise noted, the amount of the catalyst was 20 mol %. ND: not detected. NR: no reaction.

<sup>b</sup> Isolated yield.

increasing the temperature to 110 °C lowered the yield to 50% (entry 4), accompanied by a small amount of rearranged product **9a**, which could be isolated in 62% yield when conducting the reaction at 130 °C, and the yield of **11a** decreased to 15% (entry 5). After screening a wide range of solvents, DCE was turned out to be the best (entries 6–9). Several catalysts, such as CSA, ZnCl<sub>2</sub>, *p*-TsOH, and molecular sieves 4 Å, were examined (entries 10–13) and *p*-TsOH (20 mol %) provided the best yield (84%, entry 11). Therefore, the optimized combination for this reaction was to use DCE as the solvent, *p*-TsOH (20 mol %) as the catalyst, and 105 °C as the reaction temperature.

With our optimized reaction conditions, a range of R<sup>2</sup>NH<sub>2</sub> with different **6** containing various Ar and R<sup>1</sup> group were tested to investigate the reaction scope as demonstrated in Table 2. The amine structure was critical to the success of this reaction. When R<sup>2</sup> was aromatic, the reaction proceeded well, giving the desired **11** in moderate-to-good yields. In contrast, no desired product was produced when R<sup>2</sup> was an alkyl group (**11f**). Complicated reaction mixtures were obtained, when using phenylhydrazine as the amine, and the yields were lower (**11e** and **11r**). It is worth

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