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Permalink
https://escholarship.org/uc/item/9wj5f5gw

Journal
Chemistry - A European Journal, 16(27)

ISSN
09476539

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Publication Date
2010-07-19

DOI
10.1002/chem.201001075

Peer reviewed
Single Bifunctional Ruthenium Catalyst for One-Pot Cyclization and Hydration giving Functionalized Indoles and Benzofurans

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Indole[1] and benzofuran[1d,2] heterocycles are key structural units in a variety of biologically active natural products and unnatural synthetic materials. Over the last few years, transition-metal catalysts have been extensively used in the cyclization of o-alkynylarylamines[3a–l] and phenols[3m–p] to construct benzoheterocycles through intramolecular[3] and intermolecular reactions.[4] Many of these reactions required the use of a nitrogen protecting group in the case of indoles[3g,i,k] or stoichiometric amounts of the metal.[3l] McLory and Trost[3d] synthesized both unprotected indoles or N-benzyl analogues by using rhodium–phosphine complexes, but to optimize the benzofuran synthesis, large amounts of phosphine (0.6 equiv) were needed. Saa and co-workers[3q] recently reported the use of 10 mol% catalyst and amine solvents in benzofuran synthesis at 90 °C. Herein, we report that the bifunctional ruthenium catalyst 1 which has been used for anti-Markovnikov alkyn hydration[5] emerges as a versatile choice for both indole and benzofuran formation, with a number of unique advantages, including the use of only 2 mol% catalyst in most cases and the unprecedented ability of a cycloisomerization catalyst to perform hydration or deuteration in the same reaction.

We envisioned that the use of alkyn hydration catalyst 1 on substrates, such as 2 (Scheme 1) would generate the aldehyde 3, on which cyclization and dehydration would then enable facile synthesis of heterocycles. Indeed, 2a cyclized to hemiaminal 4a,[6] with some equilibrium amount of 3a, but elimination of water from 4a required heating in second step, forming 5a in 46% overall yield. The same two-step process could be used on the homologous substrate 2b, to form 5b in 56% overall yield.

Encouraged by these results, and because of the importance of indoles, we shifted our attention to substrates derived from o-ethynylaniline. The first four entries of Table 1 demonstrate that 1 cyclizes a wide range of aniline derivatives; most significantly, the simplest, unprotected parent compound 6 cyclized to indole 17 in 99% yield (Table 1, entry 1). Sulfonamide 7 (Table 1, entry 2) was cyclized to give the N-tosyl (Ts) protected indole in just 2 h. Entries 3 and 4 in Table 1 show the ability of the catalyst to form nitrogen analogues with different alkyl substituents. Especially notable is the selectivity of 1: the N-allyl group (Table 1, entry 3) is fully tolerated without the decomposition by isomerization seen when using a Rh-based catalyst.[6]

The fact that a wide variety of nucleophilic nitrogen centers could be used in indole formation encouraged us to explore the scope of 1 not only in making more complex indole derivatives, but also in cyclizing phenol derivatives to benzofurans. Gratifyingly, 1 forms both 7-aza- and 6-nitroindoles (Table 1, entries 5 and 6), showing tolerance of various ring substituents, including those that might coordinate to the catalyst. Furthermore, entry 9 (Table 1) shows the ability of 1 to form the benzofuran nucleus in essentially quantita-
Our ongoing mechanistic studies of bifunctional alkyne hydration\cite{8b} catalysts provide direct evidence for the intermediacy of vinylenes, such as B (Scheme 2). Here, indirect evidence for the intermediacy of vinylenes comes from the inertness of an internal alkyne (Table 1, entry 7) and the sluggish reaction of a silylated alkyne (Table 1, entry 8), in which the latter compound may suffer slow protodesilylation to 6 followed by rapid transformation to 17. These and all of the other cyclizations discussed below were conducted in NMR spectroscopy tubes to gain the maximum information about the course of the reaction. None of the possible hydration products of general form E (Scheme 2) were seen (estimated detection limit usually 1%). This could be a result of initial formation of E and its more rapid cyclization and water elimination to give the final product D or because of direct cyclization of vinylenes B. Evidence for the direct cyclization of B includes high yield cyclizations under anhydrous conditions (entries B in Table 1). Moreover, successful reactions of the nitro analogue 11 (entries 6A and 6B) suggest that alkyne hydration via E is not a significant pathway, because a previously attempted hydration of 4-nitro-(ethyl)benzene by using 1\cite{5a} led to the formation of less than 1% aldehyde and complete catalyst inactivation by pathways known for several other reactions of metals, alkenes, and water.\cite{6} Control experiments\cite{7} ruling out protic catalysis by using TiOH (5 mol%, 70°C, 40 h) on 6 or 14 showed that the aniline formed known\cite{8a,8b} quinoline derivative Y, whereas the phenol underwent Markovnikov hydration to give ketone Z.\cite{8c}

To further highlight the unique synthetic potential of catalyst 1, reactions on doubly ethynylated substrates 26, 27, and 28 were performed (Table 2). Of note, except for entry 2, all of the yields in Table 2 refer to isolated and purified products. The case of the nitrogen analogue 26 (entries 7A and 7B) suggested that alkyne hydration via E is not a significant pathway, because a previously attempted hydration of 4-nitro(ethyl)benzene by using 1\cite{5a} led to the formation of less than 1% aldehyde and complete catalyst inactivation by pathways known for several other reactions of metals, alkenes, and water.\cite{6} Control experiments\cite{7} ruling out protic catalysis by using TiOH (5 mol%, 70°C, 40 h) on 6 or 14 showed that the aniline formed known\cite{8a,8b} quinoline derivative Y, whereas the phenol underwent Markovnikov hydration to give ketone Z.\cite{8c}

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Scheme 2. Probable mechanism and evidence against protic catalysis (X = NH, O); conditions: a) CF₃SO₃H (5 mol%), 70°C, 40 h.

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Table 1. Results of heterocycle formation.\cite{5a,5b,6,7,8a,8b,8c}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Method[a]</th>
<th>t [h]</th>
<th>Yield[b] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9</td>
<td>17-20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6, R¹=H</td>
<td>A</td>
<td>17</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>7, R¹=Ts</td>
<td>B</td>
<td>7</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>8, R¹=allyl</td>
<td>A</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>9, R¹=allyl</td>
<td>A</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>R²=CH₂(C₂H₅)CH₂₂</td>
<td>B</td>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>R¹=allyl</td>
<td>A</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>A</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
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<td>13</td>
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<td>A</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>B[b]</td>
<td>98</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>B[b]</td>
<td>98</td>
<td>75</td>
</tr>
</tbody>
</table>

[a] See Supporting Information for substrate preparation, yield determinations, and product characterization. [b] Method A: with 5 equiv of H₂O in [D₆]acetone or [D₈]THF. Method B: no water added, in [D₆]acetone or [D₈]THF. Reactions were done on a 0.05–0.15 mmol scale with yields for the respective isolated products. NR = NMR spectroscopy integrations against an internal standard. In parentheses, the yields for the respective isolated products. [d] NR = no reaction. [e] Yields calculated from NMR spectroscopy tubes to gain the maximum information to which the latter compound may suffer slow protodesilylation to 6 followed by rapid transformation to 17. These and all of the other cyclizations discussed below were conducted in NMR spectroscopy tubes to gain the maximum information about the course of the reaction. None of the possible hydration products of general form E (Scheme 2) were seen (estimated detection limit usually 1%). This could be a result of initial formation of E and its more rapid cyclization and water elimination to give the final product D or because of direct cyclization of vinylenes B. Evidence for the direct cyclization of B includes high yield cyclizations under anhydrous conditions (entries B in Table 1). Moreover, successful reactions of the nitro analogue 11 (entries 6A and 6B) suggest that alkyne hydration via E is not a significant pathway, because a previously attempted hydration of 4-nitro(ethyl)benzene by using 1\cite{5a} led to the formation of less than 1% aldehyde and complete catalyst inactivation by pathways known for several other reactions of metals, alkenes, and water.\cite{6} Control experiments\cite{7} ruling out protic catalysis by using TiOH (5 mol%, 70°C, 40 h) on 6 or 14 showed that the aniline formed known quinoline derivative Y, whereas the phenol underwent Markovnikov hydration to give ketone Z.\cite{8c}
A moiety to the acyl could be precluded by competitive interaction with the indole NH. Consistent with this, not only did the N-methylated substrate 27 (Table 2, entry 3) cyclize to indole derivative 31 quickly, but also hydration (forming 32) was more facile, though 20 mol% catalyst was necessary (Table 2, entry 4).

In a further demonstration of the unique features of 1, the use of D₂O (Scheme 3) resulted in deuteration of indole and benzofuran at position 2 and 3,[9] which otherwise requires strong base conditions and protecting groups.[10] Literature on other alkyne hydration catalysts[11] would suggest additional roles for 1 and related species[12] in the selective labeling of organic molecules.

To summarize, compound 1 is a unique catalyst of broad application because 1) cyclic enamides, indoles, and benzofurans can be made; 2) similar low catalyst loadings are used in each case; 3) several classes of substituents are tolerated on either the benzo ring or on the nitrogen atom involved in the cyclization; 4) one-pot reactions of doubly ethynylated species can lead to significant increases in molecular complexity impossible with other cycloisomerization catalysts incapable of alkyn hydration; 5) both carbons of the newly formed heterocycle can be deuterated simply by adding D₂O. Available evidence rules out protic catalysis, but is consistent with indole and benzofuran formation from direct attack of the heteroatom, rather than water, on a vinylidene intermediate, which suggests additional applications for bifunctional catalyst 1 and its analogues in organic synthesis.

### Table 2. One-pot cyclization and hydration.a

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Method[b]</th>
<th>t [h]</th>
<th>Yield[d] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>B</td>
<td>20</td>
<td>60(^{[a]})</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>A</td>
<td>22</td>
<td>11(^{[a]})</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>B</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>A</td>
<td>24</td>
<td>95(^{[a]})</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>B</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>A</td>
<td>8</td>
<td>74</td>
</tr>
</tbody>
</table>

[a] See Supporting Information for substrate preparation, yield determinations, and product characterization. [b] Method A: with 5 equiv of H₂O, in [D₆]acetone or [D₈]THF. Method B: no water added, in dry [D₆]THF. Reactions were done on 0.2–0.5 mmol scale with 1 (4 mol%) at 70°C, unless otherwise noted. [c] Isolated and purified product. [d] Based on recovered starting material. 

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**Experimental Section**

**Preparative procedure for cyclization of 11:** In a glove box, a scintillation vial with stir bar was charged with 11 (0.0993 g, 0.6123 mmol), which was dissolved in dry and deoxygenated THF (5 mL). To this was added 1 (0.0131 g, 0.0131 mmol), the vial was sealed with its cap and the reaction mixture was subjected to heating at 70°C in an oil bath for 1 h. The reaction was monitored by TLC for complete disappearance of starting material following which the solvents were evaporated by rotary evaporation and the product was purified by column chromatography (2:1 hexanes/ethyl acetate) to give 22 as an orange solid (0.092 g, 92%).

**Preparative procedure for cyclization of 16:** In a glove box, a scintillation vial with stir bar was charged with 16 (0.0943 g, 0.535 mmol), which was dissolved in deoxygenated acetone (5 mL). To this was added 1 (0.0106 g, 0.0106 mmol), the vial was sealed with its cap and the reaction mixture was subjected to heating at 70°C in an oil bath for 1 h. The reaction was monitored by TLC for complete disappearance of starting material following which the solvents were evaporated by rotary evaporation and the product was purified by column chromatography (2:1 hexanes/ethyl acetate) to give 25 as an off-white solid (0.071 g, 75%).
Acknowledgements

The NSF is thanked for support of this work, and Dr. LeRoy Lafferty is thanked for assisting with NMR spectroscopy analysis.

Keywords: alkynes · benzofurans · deuterium · hydration · indoles


[9] Control experiments showed that neither indole nor benzofuran was deuterated at positions 2 or 3 under identical conditions, even after 168 h reaction time.


