An efficient intermolecular [Pd]-catalyzed C–C and intramolecular [Cu]-catalyzed C–O bonds formation: synthesis of functionalized flavans and benzoxepine

B. Suchand, J. Krishna, B. Venkat Ramulu, D. Dibyendu, A. Gopi Krishna Reddy, L. Mahendar, G. Satyanarayana

Department of Chemistry, Indian Institute of Technology (IIT) Hyderabad, Ordnance Factory Estate Campus, Yeddumailaram 502 205, Medak District, AP, India

Article info
Article history:
Received 27 April 2012
Revised 9 May 2012
Accepted 10 May 2012
Available online 16 May 2012

Keywords:
Flavans
[Pd]-catalysis
[Cu]-catalysis
Dihydrochalcones
Secondary alcohols

Abstract
An efficient three-step strategy for the synthesis of functionalized flavans, starting from readily available 2-bromiodobenzenes and aryl vinyl alcohols, is presented and successfully extended to benzoxepine. An intermolecular [Pd]-catalyzed C–C and an intramolecular [Cu]-catalyzed C–O bond formations have been employed as key transformations of the strategy.

Flavan is a ubiquitous 2-aryl-chroman structural unit present in a number of flavonoid natural products, which exhibit interesting biological and pharmacological activities.1 Many members of this family show interesting biological activity; for example morusyunnansin E (1) showed potent inhibitory effects on mushroom tyrosinase,2 4',6-dichloroflavan (BW683C; 2) inhibits rhinovirus replication in vitro,3 7-hydroxy-3',4'-methylenedioxyflavan (3) has been traditionally used for the treatment of diabetes, ear and chest ailments, and some viral infections,4 whereas, 4'-hydroxy-7-methoxy flavan (4) is known as one of the anti-feedant compounds in Lycoris raliata5 (Fig. 1).

Because of their unique structural features and interesting biological activities, flavans have drawn attention from many synthetic chemists. Therefore, reasonably a good number of synthetic strategies have been reported for the synthesis of flavan core structure (various chromans).6–10 Recently, transition metal promoted intramolecular [Pd]11 as well as [Cu]12-catalyzed C–O bond forming reactions between aryl halide and alcohol tether have also been developed for the synthesis of various chromans. In continuation of our interest on palladium-catalysis13 recently we disclosed an efficient and highly regio- and stereoselective [Pd]-catalyzed β-arylation method for the formation of β-arylallylic alcohols, which is unexpected under conventional Jeffery’s conditions without the assistance of silver salt. It was believed that the size of the substituent present at the ortho-position of the aromatic ring of the allylic alcohol is crucial for controlled formation of the allylic alcohol product, rather producing the expected chalcone product.13 As a result of consecutive developments for the synthesis of chalcones and their extensions, herein, we report a new efficient synthetic route for functionalized flavans (2-aryl and 2-arylmethyl substituted chromans) and a benzoxepine using two transition metals
[Pd] and [Cu]-catalyzed individual reactions as the key transformations. During the preparation of our manuscript, a closely related approach was described by Wang and Frantzén. However, our strategic approach to the precursors for key cyclization, is different from Frantzén approach and studied extensively with more number of examples (14 examples) bearing simple to electron rich functionalities on both aromatic moieties. Most significantly, the present strategy is amenable for the synthesis of benzoxepine.

Our approach for the synthesis of substituted flavans 9 and 11 is based on a key intramolecular [Cu]-catalyzed C–O bond formation between aryl bromide and tethered alcohol moieties of secondary and tertiary alcohols 8 and 10, respectively. The required precursors (secondary and tertiary alcohols) 8 and 10 can be obtained from 2-bromiodobenzenes 5, using a key intermolecular [Pd]-catalyzed C–C bond formation with allylic alcohol coupling partners 6 and followed by reduction and Grignard addition protocol, respectively (Scheme 1).

Accordingly, treatment of 2-bromiodobenzenes 5 with coupling partners allylic alcohols 6 in the presence of a catalyst Pd(OAc)$_2$ (3 mol %), PPh$_3$ (10 mol %) and Cs$_2$CO$_3$ (2 equiv) in hot acetonitrile, led to the dihydrochalcones 7 in very good (64–78%) yields. Reduction of dihydrochalcones 7 with NaBH$_4$ in methanol furnished the corresponding secondary alcohols 8 in near quantitative (97–99%) yields (Scheme 2, Table 1).

With the secondary alcohols 8 in hand, initially the key transition metal [Pd]-catalyzed C–O bond formation of the alcohol 8ca was performed under various conditions and the results are summarized in Table 2. Reaction of the alcohol 8ca with Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %) and Cs$_2$CO$_3$ (2 equiv) in hot DMF failed to furnish the product 9ca, rather exclusively furnished ketone 9ca’ (entry 1, Table 2). The formation of ketone 9ca’ can be reasoned via syn-elimination of β-hydrogen-Pd-species due to the availability of β-hydrogen, and is in good agreement with that of reported by Buchwald et al. Similarly, other catalytic variants also found to be inferior to produce the cyclic product 9ca’ (entries 2 and 4, Table 2). On the other hand, the reaction with the biaryl ligand L2, which is known to produce cyclic ethers even with secondary alcohols, produced the product 9ca in good yield 62% (entry 3, Table 2) along with the minor amount of ketone 9ca’ (9%).

Since the [Pd]-catalyzed C–O bond formation was found to be inferior, we became interested to explore the reaction conditions using [Cu]-catalyzed C–O bond formations. Gratifyingly, the initial attempt itself was found to be very efficient in the presence of catalyst CuI (20 mol %), 2,2′-bipyridyl (20 mol %), base KO’Bu (3 equiv) in hot DMF (120 °C) for 24 h on secondary alcohol 8ca and resulted exclusively the cyclized product flavan 9ca, in good yield (68%). Interestingly, the above conditions proved to be amenable for various electron releasing substituents as well on aromatic ring bearing bromide and furnished the cyclized flavan products 9 in very good yields (Table 3).

**Scheme 1.** Retrosynthetic plan for flavans 9 and 10 starting from 2-bromiodobenzenes 5.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>Yield of 7 (%)</th>
<th>Yield of 8 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>7aa 78</td>
<td>8aa 99</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>7ab 70</td>
<td>7ab 70</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>7ac 98</td>
<td>7ac 98</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>OCH$_2$</td>
<td>OCH$_2$</td>
<td>H</td>
<td>H</td>
<td>7ad 71</td>
<td>7ad 71</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>7ba 72</td>
<td>7ba 72</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>7bb 74</td>
<td>7bb 74</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>7bc 72</td>
<td>7bc 72</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>7bd 75</td>
<td>7bd 75</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>7ca 64</td>
<td>7ca 97</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields of chromatographically pure products; for compounds 7 and 8 the first letter refers to the 2-bromiodobenzenes part 5a-c whereas the second letter indicates the aromatic ring coming from the allylic alcohol 6a–6d.

**Table 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Ligand (mol %)</th>
<th>Base (equiv)</th>
<th>Yield of 9ca (%)</th>
<th>Yield of 9ca’ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (3)</td>
<td>PPh$_3$ (10)</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>—</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$ (3)</td>
<td>L1 (6)</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$ (3)</td>
<td>L2 (6)</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Pd(dba)$_3$ (3)</td>
<td>L3 (3)</td>
<td>KO’Bu (3)</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields of chromatographically pure products.
After successful accomplishment of flavans 9aa–ca, we turned our attention to determine the scope and limitation of the method. Hence, [Cu]-catalysis of tertiary alcohols 10 was also investigated. The required tertiary alcohols 10 were synthesized by the addition of alkyl/alkenyl Grignard reagents to dihydrochalcones 7, in very good yields (Scheme 3).

In general, the results were fairly comparable to those observed for secondary alcohols 8aa–ca, and furnished the products 11aa–bdm possessing simple as well as electron rich aromatic functionality on either of aromatic rings, in good yields (Table 4).

In addition to the NMR spectroscopic confirmation, the structure of one flavan was unambiguously further confirmed by single crystal X-ray diffraction analysis on 9ac (Fig. 2).

Finally to check the scope and applicability of the method, we explored the synthesis of 2-aryl-2,3,4,5-tetrahydro-1-benzoxepine (seven-membered cyclic ether). Interestingly, compounds featuring benzoxepines core are also found to be pharmaceutically important as they exhibit interesting biological activities. The requisite coupling partner, homoallylic alcohol 12a was synthesized by using Barbier reaction under sonochemical acceleration. Unlike the case of allylic alcohols, the Jeffery–Heck coupling on homoallylic alcohol 12a with 2-bromoiodobenzenes 5a, resulted in ketone 13aa in moderate yield (51%) along with a mixture of other unidentified products. Finally, [Cu]-catalyzed intramolecular C–O bond formation on the secondary alcohol 14aa, proved to be amenable to the standard conditions and gave the cyclic ether 15aa in very good yield 78% (Scheme 4).

In summary, we have developed an efficient three-step strategy for the synthesis of functionalized flavans and a benzoxepine,
employing an intermolecular [Pd]-catalyzed C–C and intramolecular [Cu]-catalyzed C–O bond formations as the key steps. The strategy is efficient and amenable for the synthesis of a number of analogs. Further investigations on the application of the current strategy for other benzoxepine analogs and for the total synthesis of flavonoid natural products are under progress.

Acknowledgments

Financial support by the Department of Science and Technology (DST), CHE/2010-11/006/DST/GSN, New Delhi is gratefully acknowledged. We thank Dr. S. J. Gharpare and Prof. Dr. Martin E. Maier for their valuable suggestions. J. K., B. V. R., A. G. K. and L. M. thanks CSIR, New Delhi, for the award of research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.050.

References and notes


