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Pd- Catalyzed Direct C-H Functionalization of Imidazolones with Aryl- and Alkenyl Halides

Mickaël Muselli, Christine Baudequin, Christophe Hoarau,* Laurent Bischoff*

Direct C-H arylation and alkenylation of 4,4'-dialkylimidazolones with a broad range of halides under palladium and copper catalysis have been developed. This methodology is applied to the preparation of recently discovered fatty acid synthetase (FAS) inhibitors.

Imidazolone is a fundamental naturally-occuring non-aromatic heterocycle intensively used in the synthesis of functional materials and pharmaceuticals. Notably, due to both small size and attractive fluorescent properties, imidazolones mostly 4-arylidene and/or 2-aryl(alkynyl)ated constitute the main cores of numerous fluorescent probes for biological studies. Among the most-representative members of this family are the green-fluorescent proteins (GFP), the Kaede protein and BODIPY-like Burgess fluorophore (figure 1).1 As recent remarkable applications in drug-design, 2-aryl(alkyl)ated imidazolones have been specifically selected for the treatment of obesity-related disorders2 and hypertension.3 They have also been found to display important biological activities4 as fatty acid synthase (FAS) inhibitors (figure 1).5

Current synthetic methodologies towards highly functionalized imidazolones that allow challenging various substitutions at 2-position are mainly based upon a ring-closing condensation of α-amidoamides (scheme 1).6 This synthetic route is fraught with the inherent difficulty in achieving highly electronically-different substrate scope so that notably, the 2-alkynylated imidazolones are mostly obtained via the 2-methyl imidazolones7 or oxazolone intermediates (scheme 1).8 Innovative synthetic methods enabling a late-stage functionalization of simple imidazolones are thus actively needed. By contrast with the structurally-related aromatic imidazole, conventional transition-metal cross-coupling reactions are however poorly appropriated due to the hard access to required 2-metallated or 2-halogenated imidazolones. To our knowledge, only the cross-coupling of 2-methylthioimidazolone has been reported.9 In this context, the discovery of direct C-H functionalization of imidazolones methodologies10,11 is particularly useful (scheme 1). Herein, the first direct C-H arylation as well as alkenylation of 4,4'-dialkylimidazolones at 2-position with aryl- and alkenyl halides are reported under Pd(0)/Cu(I) bis-catalysis.

Importantly, the activation of the imidazolone ring by prior N-oxidation is not required. This work represents a rare use of the direct C-H functionalization methodology applied to non-aromatic heterocycles.12
We started to explore the direct C-H coupling of 4,4'-cyclobutylimidazolone 1a with p-bromotoluene 2A. Indeed, any reaction occurred under the strictly Bellina’s conditions under Pd(0)/Cu(I) bis-catalysis without base and ligand assistance (Table 1, entry 1), the use of potassium carbonate base led to the desired product in 63% isolated yield (Table 1, entry 2). The reaction became fairly effective by using DBU base and the full conversion of imidazolone 1a was finally reached using PPh₃ ligand (Table 1, entry 5). The reaction remained highly operative at a slightly lower 110°C temperature, interestingly. We next investigated the generality of the optimized protocol using various arylhalides (Table 2). We found invariably that the electronic effect and the position of substituents on the aromatic unit of the halides slightly influenced the outcome of the reaction since various 2-arylated imidazolones 3aB-K flanked with trifluoromethyl, cyano, fluoro and acetamido functions were isolated in good yields. Remarkably, the procedure remained successful with aryliodides to produce imidazolones 3aA, 3aC, 3aG and 3aK in similar or better yields than those obtained using corresponding arylbromides. Moreover, reaction of 1a with p-iodobromobenzene 2K proceeded highly selectively to afford the imidazolone 3aK in good yield. The latter is useful to introduce further various substituents on the aromatic unit to design notably new precursors for biologically-active substances.

To extend the scope of this methodology, we focused on direct C-H alkenylation reaction with alkenylhalides. Interestingly, the direct C-H alkenylation of 1a with 2-bromostyrene as its pure (E)-isomer was successfully achieved applying the above optimized C-H arylation protocol. However the 2-styrenylimidazolone 5aA was isolated in poor 12% yield due to the low conversion of imidazolone 1a.

Table 1 Pd-catalyzed C-H arylation of N-benzyl-4,4'-cyclobutyl imidazolone 1a with p-bromotoluene 2A.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>T (°C)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>130</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>K₂CO₃</td>
<td>130</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Cs₂CO₃</td>
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</tr>
<tr>
<td>6</td>
<td>PPh₃</td>
<td>DBU</td>
<td>110</td>
<td>92</td>
</tr>
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<td>7</td>
<td>PPh₃</td>
<td>DBU</td>
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<td>64</td>
</tr>
<tr>
<td>8</td>
<td>PPh₃</td>
<td>DBU</td>
<td>110</td>
<td>92</td>
</tr>
</tbody>
</table>

[a] Pd(OAc)₂ (5 mol%), CuI (1 equiv), Ligand (10 mol%), Base (2 equiv), 1a (1 equiv), 2A (1 mmol), DMF (0.35M), 12 h.  
[b] Yield based on isolated product after flash chromatography.

d|

We however, switching DMF solvent to toluene along with PPh₃ to P(o-tol)₃ ligand afforded the expected cycloalkylimidazolone 5aA in 73% yield in line to our previous observations in the
A similar reactivity was observed using freshly prepared Hermann-Beller palladacycle precluding that the direct C-H alkenylation may proceed with this precatalyst readily formed by reacting Pd(OAc)₂ with P(o-tol)₃ in toluene at 80°C. Interestingly, the C-H alkenylation of 1a remained effective under steric effect when 1-iodostyrene coupling partner was used. Several bromoalkenes 4C-E were also successfully coupled with 1a to afford 2-alkenylated 5C-E in fair yields (Table 3). The scope was finally completed by the innovative production of the imidazolone 5a-F bearing an acrylamide function through full or partial reduction of the nitrile in combination with prior Michael-type addition reaction to the acrylamide system.

Table 3 Pd-catalyzed direct C-H alkenylation of 4,4'-disubstituted imidazolone 1a with alkenylbromides

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Ph</th>
<th>Br</th>
<th>Pd(OAc)₂ (5 mol%), CuI (1 equiv), P(o-tol)₃ (10 mol%), DBU (1 equiv), 1a (1 equiv), Alkenyl-Br (1 equiv), DMF (0.35 M), 110 °C, 12 h.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>5a-A, 73%</td>
<td>5a-A, 62%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>5a-B, 51%</td>
<td>5a-B, 51%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>5a-C, 49%</td>
<td>5a-C, 49%</td>
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<tr>
<td>Ph</td>
<td>Ph</td>
<td>5a-F, 30%</td>
<td>5a-F, 30%</td>
<td></td>
</tr>
</tbody>
</table>

[a] Pd(OAc)₂: (5 mol%), CuI (1 equiv), P(o-tol)₃ (10 mol%), DBU (1 equiv), 1a (1 equiv), Alkenyl-Br (1 equiv), DMF (0.35 M), 110 °C, 12 h. [b] Yield based on isolated product after flash chromatography. [c] Hermann-Beller catalyst used.

Scheme 2 Innovative access to fatty acid synthase inhibitors.

In the current context of intensive efforts in the discovery of therapeutics for the treatment of obesity-disorder, we directed the application towards an innovative synthesis of various N-alkylated 2-aryl-4,4'-cyloalkylimidazolones claimed as fatty acid synthetase inhibitors (scheme 1). First, the N-isonicotinylimidazolone 1e was successfully submitted to the optimized direct C-H arylation procedure to afford the imidazolone 3e-K in fair yield. Pleasingly, the subsequent methylation of 3e-K with iodomethane occurred only at the pyridine nitrogen. The pyridinium salt intermediate was subsequently cleanly reduced through the conventional double reduction with sodium borohydride and then dihydrogen under PtO₂ catalysis to provide the FAS inhibitor 6b in 53% yield over two-step synthesis. Furthermore interestingly, we found that the isonicotinyl protection could be fully removed. Indeed, the PtO₂-catalyzed dihydrogen reduction of the pyridinium salt intermediate provided quantitatively the unprotected imidazolone 6a previously used to prepare a wide variety of biologically active N-alkylated imidazolones.

Conclusions

As summary, we have developed an innovative and efficient synthetic methodology for direct C-H arylation and alkenylation of 4,4'-dialkylimidazolones under Pd(0)/Cu(I) bimetallic catalysis. Several electronically-different aryl- and alkenyl halides proved to be efficient coupling partners enabling a wide range of 4,4'-dialkylated imidazolones to be prepared in moderate to good yields. This novel methodology is functional group-tolerant, step-economical and highly flexible. This work represents one of first investigations in challenging direct C-H functionalization of non-aromatic heterocycles. Remarkably, the standard activation via N-oxidation is not required. This methodology may find direct applications in pharmacological and material sciences. As demonstration in this communication, an innovative and neat preparation of a recently-discovered N-alkylated 4,4'-cyloalkylimidazolone-based fatty acid synthase (FAS) inhibitor is proposed.

Acknowledgements

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Notes and references

† Electronic Supplementary Information (ESI) available: [NMR spectra and data for all compounds]. See DOI: 10.1039/b000000x/


14 See supporting information for all details.


16 The unprotected imidazolone 6a could not be produced alternatively from 3aK following standard protocols for removing the benzyl group from amide function.