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Graphical Abstract

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**sp**\(^3\) - **sp**\(^3\) Carbon-Carbon Bonds Formation using 2-Alkylazoles and a Bromoacrylate as the Reaction Partners

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sp\(^3\)-sp\(^3\) Carbon-Carbon Bonds Formation using 2-Alkylazoles and a Bromoacrylate as the Reaction Partners

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1. Introduction

Several bioactive compounds contain a 2-alkylheteroaryl motif. For example, Isavuconazole is an antifungal, Oxaprozin is a non-steroidal anti-inflammatory drug, Phenoxan is a HIV-1 inhibitor, Bendamustine is used in the treatment of lymphocytic leukemia, and Mipitroban has antithrombotic properties (Fig. 1). Therefore, the discovery of general simple routes to functionalize 2-alkyl-substituted azoles has potential for medicinal chemistry.

![Figure 1 Examples of bioactive 2-Alkylazoles derivatives.](image_url)

The palladium-catalysed direct functionalization of several (hetero)aromatics via direct sp\(^3\) and sp\(^3\)-C–H bond activation using aryl halides has brought a synthesis revolution in recent years (Scheme 1, top). Keeping in mind the results previously obtained for the direct arylation of heteroaromatics, we envisioned the assistance of a palladium catalyst for the functionalization of 2-alkylazoles with a 2-bromomethylacrylate as the coupling partner. The arylation of 2-benzylbenzimidazoles, 2-benzylbenzothiazoles or 2-benzylbenzoxazoles using aryl iodides or aryl chlorides as the coupling partners, assisted by Pd-catalysts has been reported by Oshima and co-workers (Scheme 1, top). Recently, Obora et al. reported the iridium-catalysed coupling of 2-methylbenzoxazole with benzyl alcohol for formation of sp\(^3\)-sp\(^3\) carbon-carbon bonds. The functionalization of a 2-methylbenzimidazole, deprotonated with a zinc-pivalate derivative, with ethyl 2-bromomethylacrylate as the coupling partner, catalysed by CuCN to afford the 2-[2-(benzimidazol-2-yl)-ethyl]-acrylate derivative has also been described by Knochel et al. (Scheme 1, middle). Catalyst-free reactions have attracted less attention for the functionalization of 2-alkylazoles. The reactivity of 2-alkylpyridines with 2-bromomethylacrylate in the presence of K\(_2\)CO\(_3\) as base, but without catalyst has also been described by Kim and co-workers (Scheme 1, bottom). On the other hand, to our knowledge, for 2-alkylazoles, only activated methylene...
groups, such as a 2-benzylbenzoxazole, have been functionalised without catalyst.\textsuperscript{1b,6c}

As the methods for the construction of sp\textsuperscript{3}-sp\textsuperscript{3} carbon-carbon bonds from unactivated sp\textsuperscript{3} C-H bonds of 2-alkylazoles remain scarce, the reactivity of such alkyl groups needed to be investigated. We now report conditions for the functionalization of a 2-ethyl substituent on a thiazole derivative with ethyl 2-bromomethylacrylate as the reaction partner, and show the scope of the sp\textsuperscript{3} functionalization of 2-alkyl-substituted thiazoles, imidazoles, oxazoles and pyridines.

2. Results and discussion

We initially compared the reaction of 2-ethyl-4-methylthiazole and ethyl 2-bromomethylacrylate with and without Pd-catalyst in DMA at 150 °C (Table 1). The presence of methylthiazole and ethyl 2-bromomethylacrylate with and without Pd-catalyst in DMA at 150 °C (Table 1, entry 1). The use of 2.5 equiv. of 2-bromomethylacrylate allowed to obtained 1b in 48% selectivity and in 33% yield (Table 1, entry 16). Finally, a lower reaction temperature of 110 °C affords 1a in high selectivity but in very low yield (Table 1, entry 17).

Table 1. Influence of the reaction conditions for the coupling of 2-ethyl-4-methylthiazole with ethyl 2-bromomethylacrylate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Ratio</th>
<th>Yield in 1a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>DMA</td>
<td>92:8</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>DMA</td>
<td>90:10</td>
<td>79\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>DMF</td>
<td>76:24</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>NMP</td>
<td>87:13</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>CPME\textsuperscript{b}</td>
<td>-</td>
<td>0\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>o-xylene</td>
<td>-</td>
<td>0\textsuperscript{d}</td>
</tr>
<tr>
<td>7</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>ethylbenzene</td>
<td>-</td>
<td>0\textsuperscript{d}</td>
</tr>
<tr>
<td>8</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>0\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>0\textsuperscript{c}</td>
</tr>
<tr>
<td>10</td>
<td>K\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>DMA</td>
<td>52:48</td>
<td>33 of 1b\textsuperscript{e}</td>
</tr>
<tr>
<td>11</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}(1.5)</td>
<td>DMA</td>
<td>97:3</td>
<td>&lt;10\textsuperscript{f}</td>
</tr>
</tbody>
</table>

Conditions: 2-ethyl-4-methylthiazole (1.5 mmol), ethyl 2-bromomethylacrylate (1 mmol), under argon, 16 h, 150 °C, isolated yields. \textsuperscript{a} 1 mol% PdCl(C\textsubscript{5}H\textsubscript{5})(dpbb). \textsuperscript{b} CPME: cyclopentyl methyl ether. \textsuperscript{c} 110 °C. \textsuperscript{d} 130 °C. \textsuperscript{e} 2-ethyl-4-methylthiazole (1 mmol), ethyl 2-bromomethylacrylate (2.5 mmol), K\textsubscript{2}CO\textsubscript{3} (3 mmol).

The first step of the reaction is certainly the addition of the carbonate cation has an important influence on this reaction (Table 1, entries 5-7, 9). No reaction also occurred in ethylbenzene or 1,4-dioxane in the presence of 1 mol% PdCl(C\textsubscript{5}H\textsubscript{5})(dpbb) (Table 1, entries 8 and 10). The nature of the carbonate cation has an important influence on this reaction, as both Cs\textsubscript{2}CO\textsubscript{3} and Na\textsubscript{2}CO\textsubscript{3} gave low yields of 1a (Table 1, entries 11 and 12). The low yield obtained with Na\textsubscript{2}CO\textsubscript{3} might be due to its poor solubility in DMA; whereas the higher basicity of Cs\textsubscript{2}CO\textsubscript{3} might be harmful for the reaction.

Using K\textsubscript{2}CO\textsubscript{3} as base in DMA, (Table 1, entry 1), the scope of the sp\textsuperscript{3} C-H bond functionalization using various 2-alkylthiazole derivatives was examined (Scheme 3). From 1.5 equiv. of 2,4-dimethylthiazole and 1 equiv. of ethyl 2-bromomethylacrylate, a mixture of 2a and 2b was obtained in a 19:81 ratio. The use of a...
larger excess of 2,4-dimethylthiazole (3 equiv.) did not allowed to obtain 2a in good selectivity. Again, no sp\(^3\) C-H bond functionalization at position C4-Me thiazole was observed. On the other hand, the reaction of 2-butylthiazole or 2-i-propylthiazole (1.5 equiv.) with ethyl 2-bromomethylacrylate (1 equiv.) led exclusively to mono-coupling products 3a and 4a in moderate to high yields. Then, we studied the influence of benzene substituents of 2-butyl-5-aryltiazoles for such couplings (Scheme 3). Nitro-, chloro- or cyano- substituents are tolerated to afford couplings (Scheme 3). Nitro-, chloro- or cyano- substituents are tolerated to afford mono-coupling products 5a, 6a and 8a in 51-66% yields. The highest yield was obtained from 2-i-propylthiazole (1.5 equiv.) with ethyl 2-bromomethylacrylate (1 equiv.) led exclusively to mono-coupling products.

The reactivity of a few 2-alkylpyridine derivatives using K\(_2\)CO\(_3\)/DMA as reaction conditions was also studied (Scheme 6). A mixture of 1 equiv. of ethyl 2-bromomethylacrylate and 1.5 equiv. of 2-methylpyridine gave the products 19a and 19b in a 84:16 ratio. Under similar conditions, the coupling with 2,3-dimethylpyridine only gave 19a in a very high yield. A high selectivity in favour of the formation on mono-coupling product 21a was also observed with 2,4-dimethylpyridine.

The influence of the nature of the heteroatom at position 1 of the heteroarene was also examined (Scheme 5). The reaction of 1.5 equiv. of 1,2-dimethylimidazole with 1 equiv. of ethyl 2-bromomethylacrylate only gave mono-coupling product 14a in 71% yield. Similarly, 1-benzyl-2-methylimidazole only afforded the mono-coupling product 15a in 65% yield. On the other hand, a mixture was obtained from 1-decyl-2-methylimidazole with the formation of 16a and 16b in a 82:18 ratio. However, the use of a larger excess of 1-decyl-2-methylimidazole gave 16a in 99% selectivity and 78% yield. From both 2,4,5-trimethoxyoxazole and 2-ethyl-4,5-dimethoxyoxazole (3 equiv.), again the formation of mixtures of mono- and di-alkylation products 17a:17b and 18a:18b in 47:53 and 45:55 ratios was observed.
Acknowledgments

We are grateful to the “Chinese Scholarship Council” for a grant to Z. L.

References and notes


11. For a review on thermal and palladium-catalysed aza-Cope rearrangement, see: Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. Synthesis 2009, 2117-2142.


13. General procedure for the synthesis of 1a-2a: As a typical experiment, reaction of the heterocyclic (1.5 mmol) ethyl 2-bromomethylacrylate (0.193 g, 1 mmol), K₂CO₃ (0.207 g, 1.5 mmol) at 150 °C during 16 h in DME (4 mL) under argon afforded the corresponding products after extraction with dichloromethane, evaporation and filtration on silica gel. All compounds gave satisfactory 1H, 13C and elementary analysis.

14. Ethyl 2-[2-(4-methylthiazol-2-yl)-propyl]-acrylate (1a) H NMR (400 MHz, CDCl₃): δ 6.64 (s, 1H), 6.10 (s, 1H), 5.43 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.45-3.30 (m, 1H), 2.77 (dd, J = 13.9, 7.1 Hz, 1H), 2.56 (dd, J = 13.9, 7.1 Hz, 1H), 2.35 (s, 3H), 1.29 (d, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl₃): δ 175.2, 166.9, 152.0, 138.1, 127.3, 112.0, 60.7, 39.8, 37.4, 20.9, 17.0, 14.2. Ethyl 4-methyl-2,6-dimethylene-4-(4-methylthiazol-2-yl)-heptane-1,6-diol (1b) was also isolated: 1H NMR (400 MHz, CDCl₃): δ 6.63 (s, 1H), 6.04 (s, 2H), 5.19 (2H), 4.10-4.00 (m, 4H), 2.91 (d, J = 13.2 Hz, 2H), 2.78 (d, J = 13.2 Hz, 2H), 2.37 (s, 3H), 1.23 (s, 3H), 1.18 (t, J = 7.1 Hz, 6H). 13C NMR (100 MHz, CDCl₃): δ 177.0, 151.9, 137.0, 128.5, 112.5, 60.7, 45.1, 42.7, 22.7, 17.1, 14.1.