PALLADIUM CATALYZED COUPLING OF 5-HYDROXYURACIL TRIFLUOROMETHANE-SULFONATES (TRIFLATES) WITH ALKENES AND ALKYNES

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Abstract - Cross coupling of 5-hydroxyuracil triflates (1) with alkenes and alkynes in the presence of a palladium catalyst and triphenylphosphine affords 5-vinyluracils (2) and 5-alkynyluracils (3), respectively, in good yields. Coupling of the triflate (1a) with organocopper reagents \([R_2Cu(CN)Li_2]\) is also described.

The palladium catalyzed reaction of vinyl or aryl triflates has been extensively studied as one of the efficient approach to carbon-carbon bond formation.¹ To our best knowledge, no example of palladium catalyzed vinylation and alkylnylation of heterocyclic triflates has been appeared in the literatures.²³ We attempted the application of this type of reaction to 5-hydroxyuracil triflates because some 5-carbon substituted uracil derivatives have interesting biological activities.³ The present result provides a novel method⁴ for the preparation of uracil derivatives possessing the carbon functional groups at the 5-position, which is the first demonstration of the C-C coupling of heterocyclic triflates.

The 5-hydroxyuracil triflates (1a and 1b),⁵ employed here as starting materials, were prepared in 99% and 54% yields, respectively, upon treatment of the corresponding 5-hydroxyuracils⁶ with trifluoromethanesulfonic anhydride in dry pyridine under ice cooling.

A mixture of the triflate (1a) [1 mM], methyl acrylate [1.5 mM], triethylamine [2 mM], palladium chloride [0.02 mM], and triphenylphosphine [0.04 mM] in dry dimethylformamide was heated at 60-70 °C for 6 h. After removal of the solvent, the residue was triturated with water. The mixture thus obtained was extracted with chloroform to obtain 5-(2-E-methoxycarbonyl)vinyl-1,3-dimethyluracil (2a) in 76% yield. No formation of other products (e.g. (Z)-isomer of 2a) in this reaction was shown by T.L.C. analysis of the reaction mixture and ¹H-NMR spectrum of...
Table. Formation of 5-Vinyluracils (2) and 5-Alkynyluracils (3)

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Alkene or alkyne</th>
<th>Reaction time (h)</th>
<th>Product</th>
<th>mp (°C) (Recryst. solvent)</th>
<th>Yield(%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>CH₂=CH·CO₂CH₃</td>
<td>6</td>
<td>2a</td>
<td>165-167 (CH₃OH)</td>
<td>76</td>
</tr>
<tr>
<td>la</td>
<td>CH₂=CH·COC₃H₅</td>
<td>12</td>
<td>2b</td>
<td>164-166 (C₂H₅OH)</td>
<td>96</td>
</tr>
<tr>
<td>la</td>
<td>CH₂=CH·CN</td>
<td>5</td>
<td>2c</td>
<td>165-166 (C₂H₅OH)</td>
<td>93</td>
</tr>
<tr>
<td>la</td>
<td>CH₂=CH·C₆H₅</td>
<td>5</td>
<td>2d</td>
<td>144-146 (C₂H₅OH)</td>
<td>95</td>
</tr>
<tr>
<td>lb</td>
<td>CH₂=CH·CO₂CH₃</td>
<td>5</td>
<td>2e</td>
<td>272-274 (CH₃OH)</td>
<td>88</td>
</tr>
<tr>
<td>la</td>
<td>CH≡C·CH₂OH</td>
<td>3</td>
<td>3a</td>
<td>201-203 (C₂H₅OH)</td>
<td>72</td>
</tr>
<tr>
<td>la</td>
<td>CH≡C·C₆H₅</td>
<td>3</td>
<td>3b</td>
<td>157-158 (C₂H₅OH)</td>
<td>83</td>
</tr>
<tr>
<td>la</td>
<td>CH≡C·Si(CH₃)₃</td>
<td>2.5</td>
<td>3c</td>
<td>160-162 (C₂H₅OH)</td>
<td>59</td>
</tr>
</tbody>
</table>

* Isolated yields.

the crude product. The coupling reaction did not proceed in the absence of palladium chloride and triphenylphosphine.

Analogous coupling reaction of la with other alkenes such as methyl vinyl ketone,
acrylonitrile, and styrene gave the corresponding 5-vinyluracils (2b–2d) in high yields. The 5-hydroxy-1-methyluracil triflate (1b), which possesses no substituent at the 3-position, also reacted with methyl acrylate to give a coupling product (2e). All results of the vinylation of 1a and 1b are summarized in Table. The trans configuration of the vinyl group of 2a–e was determined on the basis of a large coupling constant (16 Hz) in the $^1$H-NMR spectrum.

When the methanesulfonate (4) of 5-hydroxy-1,3-dimethyluracil was used instead of the triflates (1) in the palladium-catalyzed coupling reaction, the sulfonate (4) was recovered unchanged. This result indicates that the O-triflate function is an excellent leaving group for the palladium catalyzed C-C coupling reaction.

Treatment of 1a with alkynes such as 2-propyn-1-ol, phenylacetylene, and trimethylsilylacetylene in the presence of palladium acetate, triphenylphosphine, triethylamine, and copper iodide resulted in the formation of the 5-alkynyluracils (3a–c) in good yields (see Table).

Direct introduction of an alkyl group into the 5-position of uracil derivatives has been scarcely investigated. Thus, coupling of the triflate (1a) with organocuprate $[\text{R}_2\text{Cu(CN)Li}_2]$ in the absence of a palladium catalyst was examined. When the triflate (1a) was treated with $\text{Me}_2\text{Cu(CN)Li}_2$ in tetrahydrofuran under argon atmosphere, the expected thymine derivative (5a) was obtained in 71% yield. On the other hand, analogous coupling of 1a with $\text{Bu}_2\text{Cu(CN)Li}_2$ led to the formation of 5-butyl-1,3-dimethyluracil (5b), 6-butyl-1,3-dimethyluracil (6), and 1,3-dimethyluracil in 20%, 10%, and 29% yields, respectively.

REFERENCES AND NOTES
5. All new compounds (1-4 and 6) gave satisfactory microanalytical results and spectral data consistent with the assigned structures.
7. The use of palladium acetate instead of palladium chloride as a catalyst resulted in the improvement of the yield in some extent.
8. A catalytic amount of copper iodide was used. The absence of copper iodide in this reaction extremely reduced the yield of the coupling product.
10. Organocuprates \([R_2Cu(CN)Li_2]\) were prepared in situ from copper cyanide (1 eq.) and alkyl lithium (2 eq.); B. H. Lipshutz and R. S. Wilhelm, J. Am. Chem. Soc., 1981, 103, 7672.

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