promoting access to White Rose research papers

Universities of Leeds, Sheffield and York
http://eprints.whiterose.ac.uk/

This is a copy of the final published version of a paper published via gold open access in Chemistry - A European Journal.

This open access article is distributed under the terms of the Creative Commons Attribution Licence (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/83927

Published paper

Cycloaddition

Development of a Mild and Versatile Directed Cycloaddition Approach to Pyridines

Sylvestre P. J. T. Bachollet, Jérôme F. Vivat†, Dean C. Cocker, Harry Adams, and Joseph P. A. Harrity*[a]

In memory of Jérôme F. Vivat

Abstract: The aza-Diels–Alder cycloaddition of 1,2,4-triazines with alkynes offers a rapid and convenient method for the synthesis of highly substituted pyridines, but often requires harsh conditions and long reaction times. The present study offers a solution to these limitations by use of a temporary tether established by a Lewis acid–base complexation of in situ generated alkynylboranes and triazines bearing a Lewis basic donor. The cycloaddition reactions take place within 20 min at 40 °C and provide direct access to a broad range of pyridines with complete and predictable regiocontrol. The carbon–boron bond can be further functionalised by cross-coupling allowing further functionality to be introduced after cycloaddition.

Introduction

Pyridines are a fundamentally important class of aromatic molecules.[1] They are present in many bioactive compounds and they play a key role in a number of biological processes. From a synthetic viewpoint, the ready quaternisation of the basic pyridine ring limits the functionalisation of this aromatic system by electrophilic substitution processes. Ring substitution is, therefore, often dictated by the availability of a halide substituent, or related group that allows elaboration by substitution or transition-metal-catalysed coupling. An alternative approach to pyridines is by means of ring synthesis and a number of approaches are now established.[2] In this regard, the inverse electron demand aza-Diels–Alder reaction of triazines constitutes a useful and much studied method, however this process has largely focused on the use of enamine dienophiles as alkyne surrogates because alkynes themselves only participate in [4+2] cycloadditions with triazenes under very harsh conditions. Moreover, such processes are often poorly regioselective and are relatively low yielding.[3]

With regard to inverse electron demand aza-Diels–Alder reactions, we have recently become interested in the use of directed cycloadditions for the mild and regiocontrolled synthesis of aromatic and heteroaromatic compounds.[4] Central to our design was the use of an alkyne bearing a Lewis acid acceptor that would promote pre-association with a diene bearing a complementary Lewis base (Scheme 1). The resulting complex would provide a platform for rate enhancements in the ensuing cycloaddition, and this rate enhancement was exemplified by the reaction of tetrazines with in situ generated alkynyltriﬂuoroboranes at ambient temperatures.

In considering an appropriate alkyne-substituted Lewis acid, boron-based acceptors are of particular interest as they deliver organoboron products of potential value for further organic synthesis.[5] We report herein the employment of this concept in a mild and versatile route to pyridine boronic acid derivatives by means of directed triazine cycloadditions.
Results and Discussion

To establish a typical reactivity profile for non-activated triazines and alkynes, we opted to explore the cycloaddition reactions of readily available alkynes and triazine. Indeed, we found that triazine 1a was particularly reluctant to undergo efficient reaction with phenylacetylene, providing the corresponding product in low yield after prolonged heating, albeit with high regiocontrol. Moreover, we attempted a similar reaction with an alkynylboronate and found that this approach generated the corresponding pyridine boronic acid derivative, again in very low yield, but with high regioselectivity (Scheme 2).

The poor reactivity of diene 1a with alkynes made it an ideal choice for evaluating the potential of our proposed directed cycloaddition, and we set out to explore the reaction of this compound with alkynytrifluoroborate 2a, our results are depicted in Table 1. Fluorophilic Lewis acids are known to transform alkynytrifluoroborate salts into the corresponding difluoroboranes, and so we employed BF$_3$·OEt$_2$ to promote formation of our BF$_2$-appended alkyne in situ. Remarkably, simply stirring this Lewis acid and substrate combination in CH$_2$Cl$_2$ at room temperature provided the desired cycloadduct (entry 1). The yield could be improved by increasing the temperature and the concentration of alkynydifluoroborane (entries 2 and 3). Finally, TMSCl was also found to be a competent fluorophile, albeit slightly less effective than BF$_3$·OEt$_2$ in this case (entry 4). Confirmation of the Lewis acid–base interaction between the pyridyl and BF$_2$ substituents in the product, as well as the regioselectivity, was confirmed by X-ray crystallography. Figure 1 shows the expected tetrahedral geometry around the B atom.

A minor side product observed in the cycloadditions of 1a and 2a was the product of direct acetylide addition at the heteroaromatic ring. This compound was isolated in 12% yield under the optimal conditions (Table 1, entry 3), and its structure was also verified by X-ray crystallography (Figure 2).

Notwithstanding the propensity for competing direct addition processes, the optimal conditions of the cycloaddition were found to be quite general across a small selection of alkynes, allowing the corresponding pyridines 5–7 to be generated in moderate to high yield (Figure 3).

### Table 1. Directed cycloaddition of 1 and alkynytrifluoroborates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid[a] (equiv)</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Yield 3 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$·OEt$_2$ (2)</td>
<td>25</td>
<td>16 h</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$·OEt$_2$ (2)</td>
<td>40</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$·OEt$_2$ (3)</td>
<td>40</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>Me$_3$SiCl (3)</td>
<td>40</td>
<td>10</td>
<td>73</td>
</tr>
</tbody>
</table>

[a] A 1:1 stoichiometry of Lewis acid and alkyne was used in all cases.

**Figure 1.** X-ray crystal structure representation of 3, H atoms omitted for clarity.

**Figure 2.** X-ray crystal structure representation of 4.

**Figure 3.** Pyridine products from the directed cycloaddition of 1a. Conditions: 1a (1 equiv), alkyne (3 equiv) and BF$_3$·OEt$_2$ (3 equiv) heated at 40°C in CH$_2$Cl$_2$ for 10 min.
Having established reaction conditions for the mild cycloaddition of triazine 1a with alkynyltrifluoroborates, we set out to explore the scope of this chemistry for the preparation of bipyridyldifluoroboranes, our results are shown in Table 2. We began by employing an isomer of triazine 1a and were pleased to find that pyridines 8 and 9 were formed in high yield (entries 1 and 2). Expanding to more heavily substituted triazines provided the opportunity to access fully substituted pyridines under mild conditions (entries 3–6). This approach is completely regioselective because of the nature of the direct-ed reaction; therefore, this approach represents a powerful method for assembling highly functionalised products with entirely predictable regiocontrol. Finally, less heavily substituted pyridines can also be accessed by this strategy, compounds 14 and 15 were both prepared from triazine 1e in good yield.

Having had broad success with pyridyl directing groups, we decided to establish whether other Lewis bases could direct the cycloaddition reaction. Indeed, we were pleased to find that amidcs also functioned as competent directing groups, providing access to pyridines 16–20 in good overall yield (Scheme 3). Interestingly, the less substituted triazine substrate 1h was significantly less efficient, providing poor yields of the corresponding pyridines even when the reaction was conducted at low temperature. In this case, the crude mixtures were relatively complex, but the major side product in each case, 24, appeared to result from alkyne addition to the ring.[11]

A further issue that we wished to clarify was the importance of the positioning of the directing group. In principle, the Lewis basic donor could also be incorporated at the 6-position of the triazine giving rise to isomeric pyridine products. As shown in Scheme 4, the cycloaddition of 25 was found to proceed in good yield, although the reaction required a longer time period and returned a small amount of starting triazine 25 (≈10%). We also prepared 27 to probe the effect of having two competing directing groups on reaction regiochemistry. Interestingly, the reaction proceeded with high selectivity to provide 28a, albeit in modest yield,[12] and <5% of regioisomer 28b (as judged by LC-MS analysis). This preliminary data suggest that substrates bearing a direct-ing group at the 3-position are optimal, but that the inclusion of directing groups at C6 are viable. Further studies aimed at understanding the scope of di-

### Table 2. Directed cycloaddition of triazines and alkynyltrifluoroborates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Triazine</th>
<th>Alkyne (R')</th>
<th>Product</th>
<th>Lewis acid[a]</th>
<th>Yield 3a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph; 2a</td>
<td>R=Ph; 2a</td>
<td>Me3SiCl (3)</td>
<td>R=Ph; 75 (8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph; 2b</td>
<td>R=C6H9; 8 3</td>
<td>Me3SiCl (3)</td>
<td>R=C6H9; 83 (9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph; 2a</td>
<td>R=Ph; 8,9</td>
<td>BF3·OEt2 (3)</td>
<td>R=Ph; 72 (10)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph; 2a</td>
<td>R=Ph; 10,11</td>
<td>BF3·OEt2 (3)</td>
<td>R=C6H9; 76 (11)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bu; 2c</td>
<td>R=Ph; 12</td>
<td>BF3·OEt2 (3)</td>
<td>R=Bu; 82 (12)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bu; 2c</td>
<td>R=Bu; 13</td>
<td>BF3·OEt2 (3)</td>
<td>R=Bu; 62 (13)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Bu; 2c</td>
<td>R=Bu; 14,15</td>
<td>Me3SiCl (3)</td>
<td>R=Bu; 62 (15)</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 3. Alternative directing groups. [a] The reaction was conducted at 40°C for 20 min.
Cross coupling of two representative difluoroboranes, 9, acceptable yields (Scheme 5).

Although the main objective of this study was to demonstrate that the directed cycloaddition could deliver faster reactions than the traditional aza-Diels–Alder process, we recognised the potential value of the products that are armed with directing-group positioning are currently being pursued.

We have developed a mild and regiocontrolled method for the synthesis of highly substituted pyridines by means of a Lewis base directed cycloaddition of triazines and in situ generated boron bond coupling reactions.

Experimental Section

General procedure for the cycloaddition of alkynyltrifluoroborates and triazines

Synthesis of 3: A solution of 6-phenyl-3-(2-pyridyl)-1,2,4-triazine 1a (50 mg, 0.21 mmol) and potassium (phenylethynyl)trifluoroborate 2a (132 mg, 0.64 mmol) in CH2Cl2 (2 mL) was treated with BF3·OEt2 (55 µL, 0.64 mmol). The reaction was stirred for 10 min and then quenched with brine (10 mL). The mixture was extracted with CH2Cl2 (3 × 15 mL) and the extract dried over MgSO4, filtered and the solvent evaporated. The residue was purified chromatographically over silica gel (gradient; starting with petroleum ether, ending with ethyl acetate) to afford 3-(difluoroboryl)-4,5-diphenyl-2-dicyclohexylphosphino·boronate 3 (63 mg, 84%) as a colourless solid. m.p 225–226°C. 1H NMR (400 MHz, CDCl3): δ = 7.18–7.22 (2H, m), 7.25–7.33 (6H, m), 7.35–7.40 (2H, m), 7.61–7.67 (1H, m), 8.26 (1H, td, J = 7.5, 1.5 Hz), 8.40 (1H, d, J = 8.0), 8.59 (1H, d, J = 5.5 Hz). 8.67 ppm (1H, s); 13C NMR (100.6 MHz, CDCl3): δ = 118.9, 125.0, 127.4, 127.7, 127.8, 127.9, 128.2, 129.8, 129.9, 138.2, 138.5, 141.4, 144.1, 145.7, 151.9, 154.6, 154.9 ppm; 19F NMR (235.1 MHz, CDCl3): δ = 156.4 ppm; FTIR: ν = 3058 (w), 2925 (w), 1626 (s), 1578 (m), 1555 (m), 1489 (s), 1452 (m), 1343 (s), 1158 (m), 1131 (s), 1100 (s), 1007 (m), 910 cm⁻¹. HRMS: (ESI) m/z calcd for C22H15BF2N2Na: 379.1194 [M+Na⁺], found 379.1204.

Acknowledgements

This work was supported by The University of Sheffield, the EPSRC and the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012-316379).

Keywords: boranes • cycloadditions • pyridines • regioselectivity • triazines

Conclusion

We have developed a mild and regiocontrolled method for the synthesis of highly substituted pyridines by means of a Lewis base directed cycloaddition of triazines and in situ generated alkynylboranes. This method proceeds with a range of alkynes and triazines, although it appears to be advantageous to have the Lewis base directing group at C3 of the diene cycloaddition partner. As well as providing a convenient means for generating bipyridines, this method is compatible with amide directing groups and the presence of the carbon–boron bond allows further functionalisation to take place through cross-coupling reactions.

Alkynyl difluoroboranes are subject to rapid and reversible disproportionation to dialkynyl fluoroboranes and trialkynylboranes, which can all undergo cycloaddition. Nonetheless, these products can all converge to the corresponding difluoroboranes products following further disproportionation. For a discussion, see: D. F. P. Crépin, J. P. A. Harrity, J. Jiang, A. J. H. M. Meijer, A.-C. M. A. Nassoy, P. Raubo, J. Am. Chem. Soc. 2014, 136, 8642.


[9] Compound 24, R = Ph was characterised by $^1$H, $^{13}$C NMR and HRMS analysis, whereas R = Bu was tentatively characterised by $^1$H NMR and HRMS analysis only.

[10] CCDC-1005645 (4), 1005646 (17), 1005647 (3) and 1005648 (28a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: June 11, 2014
Published online on August 21, 2014