This is a repository copy of A Mild and Regiospecific Synthesis of Pyrazoleboranes.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/113892/

Version: Accepted Version

Article:

https://doi.org/10.1002/chem.201701019

This is the peer reviewed version of the following article: Harrity, J. P.A. et al (2017), A Mild and Regiospecific Synthesis of Pyrazoleboranes. Chem. Eur. J., which has been published in final form at https://doi.org/10.1002/chem.201701019. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Reuse
Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.
A Mild and Regiospecific Synthesis of Pyrazoleboranes

Andrew W. Brown, Júlia Comas-Barceló and Joseph P.A. Harrity*

Pyrazoles are commonly employed in the discovery of pharmaceuticals and as crop protection agents.\(^1\) Therefore, methods that allow these compounds to be readily prepared and functionalized are of significant value. However, synthetic approaches to these diazoles can be non-trivial and often result in the formation of isomeric mixtures.\(^2\) Dipolar cycloaddition strategies offer a convenient way to access complex pyrazoles from simple substrates, and this approach is widely used. In this context, the [4 + 2] cycloaddition/retro-cycloaddition of alkynes and sydnones can be particularly effective, as unlike most dipolar reagents, sydnones are bench stable compounds that can be easily generated and stored under ambient conditions for long periods.\(^3\)

Despite widespread interest in the utilization of sydnones for pyrazole synthesis,\(^4\) significant challenges persist with respect to the reaction conditions. Indeed, the synthesis of fully-substituted pyrazoles via the reaction of unsymmetrical internal alkynes and 4-substituted sydnones is currently very limited, with relatively few examples, all of which require high reaction temperatures, long reaction times and which often deliver poor reaction regiocontrol.\(^5\) Studies in our group have focused on the cycloaddition of sydnones with alkynyl boronic esters to address this limitation.\(^6\) However, while good regiocontrol can be achieved in some cases, the reactions require temperatures >140°C over extended reaction times (>24 h). A representative example that illustrates this point is shown in Scheme 1. Attempts to prepare bioactive pyridylpyrazoles\(^7\) by cycloaddition/cross-coupling methods were hampered by low yields encountered during the key cycloaddition step.

We began our investigations by studying the cycloaddition reaction of 4-pyridylsydnone \(1\) and the alkynyl trifluoroborate derived from 1-octyne. Preliminary experiments showed that the use of 3 equivalents each of alkyne and Lewis acid provided the corresponding pyrazole under ambient conditions and within 3 h in 54% yield (Table 1, Entry 1). A particularly surprising feature of the reaction was that we only observed dialkynylborane \(2\) rather than the expected difluoroborane \(3\). Reducing the equivalents of Lewis acid had no noticeable effect on reaction conversion (Entry 2), and increasing reaction time to 24 h or steadily increasing the number equivalents of alkyne also failed to improve conversion to pyrazole (Entry 3). As the reaction formally requires a 3:1 stoichiometry of \([\ast]\) A.W. Brown, J. Comas-Barceló, Prof. J.P.A. Harrity
Department of Chemistry
University of Sheffield
Sheffield, S3 7HF (UK)
Fax: (+44) 114-222-9346
E-mail: j.harrity@sheffield.ac.uk

[\ast\ast]\) This work was supported by Cancer Research UK and Yorkshire Cancer Research and the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012-316379).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

[\ast\ast]\) This work was supported by Cancer Research UK and Yorkshire Cancer Research and the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012-316379).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1. Preliminary cycloaddition studies and optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. BF(_3)</th>
<th>Equiv. alkyne</th>
<th>Conversion[^a[^b]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>3.0</td>
<td>65% (54%)</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>5.0</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>5.0</td>
<td>100% (100%)</td>
</tr>
</tbody>
</table>

[^a]\) Conversion estimated by 400 MHz \(^1\)H NMR spectroscopy. [^b]\) Isolated yields in parenthesis. equivalents of alkyne also failed to improve conversion to pyrazole (Entry 3). As the reaction formally requires a 3:1 stoichiometry of
alkyne:BF$_3$-OEt$_2$ for complete conversion to 2, it is perhaps unsurprising that increasing the number of equivalents of alkyne but not Lewis acid did not affect conversion. However, it is notable that this variation in stoichiometry did not lead to other borane-containing pyrazoles (i.e., mono- or di-fluoroboranes) either. Finally, increasing the equivalents of Lewis acid in the presence of 5 equivalents of trifluoroborate salt provided a significant improvement in conversion, allowing the isolation of pyrazole 2 in quantitative yield after 2 hours (Entry 4). This study therefore confirmed that fully-substituted pyrazoles could be accessed from sydnones within a few hours under ambient conditions for the first time. This result represents a significant rate acceleration in these reactions, and offers a mild and regiocontrolled means for accessing functionalized pyrazoles.

With optimal conditions in hand, we turned our attention to investigating the reaction scope (Table 2). Beginning with the nature of the sydnone N-substituent, we were pleased to find that both aromatic and aliphatic groups were tolerated, providing the corresponding pyrazoles 4-7 in high yield (entries 1-4). This methodology is therefore especially well suited to the cycloaddition of N-aryl sydnones, which are typically more stable and less reactive than the N-aryl analogs and often perform poorly in cycloadditions. To further demonstrate the versatility of the chemistry, the cycloaddition scope with respect to the alkyne trifluoroborate salts was undertaken (entries 5-9). We found the reaction to be tolerant of a selection of substituent types including aryl, alkenyl, tert-alkyl, silyl and the corresponding terminal alkyne. The regiochemistry of formation of 9 is especially noteworthy as the 1,4,5-trisubstituted pyrazole borane substitution pattern complements the natural 1,3,5-substitution observed in thermally promoted reactions of sydnones and terminal alkynylboronates.

Table 2. Pyrazole synthesis scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sydnone</th>
<th>R$^1$, R$^2$</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4-FC$_2$H$_4$, C$_6$H$_5$</td>
<td>4; 85%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4-MeOCH$_2$H$_4$, C$_6$H$_5$</td>
<td>5; 99%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-FC$_2$H$_4$, C$_6$H$_5$</td>
<td>6; 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-FC$_2$H$_4$, C$_6$H$_5$</td>
<td>7; 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Ph, Ph</td>
<td>8; 100%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>Ph, H</td>
<td>9; 78%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>Ph, t-Bu</td>
<td>10; 81%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>Ph, C(Me)=CH$_2$</td>
<td>11; 72%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>Ph, SiMe$_3$</td>
<td>12; 61%</td>
<td></td>
</tr>
</tbody>
</table>

Finally, we explored the effect of the directing group on the reaction (Scheme 3). Gratifyingly, incorporation of a methyl group at all positions on the pyridine ring did not have a significant effect on reactivity and boranes 13-16 were all formed in high yield. Both electron donating and electron withdrawing groups were tolerated, and the reaction was successfully extended to include a quinoline and an oxazine directing group, all of which afforded the corresponding pyrazoles 17-20 in excellent yield. In contrast, the oxazoline substituted sydnone did not afford the expected cycloadduct 21. In this case, the borane appeared to be sensitive towards protodeborylation such that the alkyne moieties were cleaved upon workup and purification to deliver the corresponding boronic acid 22 which was isolated in low yield. Finally, we were surprised to find that amide 23 did not promote cycloadditions as this had previously proven to be a rather general directing group.

Scheme 3. Directing group scope. [a] Reaction conducted over 4 h.

The regiochemistry of the reaction was unambiguously confirmed by X-ray crystallography in the case of pyrazole 8, and other substrates were assigned by analogy. The crystal structure confirmed the existence of a bonding interaction between the pyridine nitrogen and boron.

After demonstrating the versatility of the chemistry in accessing a broad library of pyrazole dialkynylboranes, we sought to demonstrate that the dialkynylborane motif could be used as handle for functionalization. To the best of our knowledge, the reactivity of...
this unusual motif has never been investigated. We first sought conditions for protodeboronation. Pleasingly, heating 2 in THF/H₂O in the presence of sodium carbonate furnished 24 in excellent yield (Scheme 4). We next turned our attention to oxidation. Gratifyingly, gentle heating of 2 with hydrogen peroxide afforded phenol 25 in good yield. We were also pleased to find that heating 2 with pinacol and caesium carbonate furnished the pinacol ester 26 in excellent yield, even when carried out on 0.5 g scale. Finally, we found 2 to be a rather demanding substrate for Suzuki-Miyaura coupling. However, the use of the 2nd generation XPhos precatalyst successfully promoted formation of cross-coupled product 27 using 4-bromoanisole.

Overall therefore, the experimentally observed directed cycloaddition reaction of sydnones and alkynylboranes was found to proceed under mild conditions and in high yields. A number of unexpected observations were made during the course of these studies; i) the strategy is successful for a number of pyridine based directing groups; ii) directing group ring size may be important; whilst 1,3-oxazines are effective, the corresponding 1,3-oxazolines and oxazoles are poor directing groups; iii) amides do not promote the cycloaddition process; iv) the products are generated as dialkynylboranes with no trace of the corresponding difluoroboranes. The products are probably formed via disproportionation of the in situ generated alkynyldifluoroborane followed by cycloaddition,[9] although the lack of further disproportionation to difluoroboranes is unexpected. In order to understand the surprising differences observed in this study, both theoretical and mechanistic investigations have been undertaken and these will be reported elsewhere.

In conclusion, sydnones bearing pyridines and related azines at C4 undergo rapid cycloaddition with alkynylboranes to generate pyrazoleboranes with complete control of regioselectivity. These reactions proceed under ambient conditions, demonstrating unprecedented reactivity for the [4 + 2] cycloaddition of sydnones with simple alkenes. The pyrazoleboranes undergo typical organoboron functionalization reactions such as oxidation and cross-coupling, confirming the value of these products for organic synthesis.

**Experimental Section**

Typical cycloaddition procedure as exemplified by the formation of 8: to a suspension of 1 (50 mg, 0.21 mmol) and potassium(1-phenylethyn-2-yl)trifluoroborate (218 mg, 1.05 mmol) in dichloroethane (1 mL, 0.2 M) under an atmosphere of nitrogen at 25 °C was added a solution of BF₃·OEt₂ (60 mg, 0.42 mmol) in dichloroethane (1 mL, 0.4 M). The reaction was stirred for 2 hours at 25 °C before brine was added. The resulting mixture was extracted with dichloromethane and the combined organic layers dried over MgSO₄, filtered through a short pad of celite and concentrated in vacuo. Flash silica chromatography (gradient starting with 100% 40-60 petroleum ether and ending with 40% ethyl acetate in 40-60 petroleum ether) afforded 8 as a tan solid (107 mg, 100%). M.p.: 246-248 °C (dec.); 1H NMR (400 MHz, CDCl₃) δ 7.15-7.23 (6H, m), 7.29-7.54 (10H, m), 7.59 (2H, t, J = 8.5 Hz), 7.65-7.72 (2H, m), 7.90-7.99 (1H, m), 8.39 (2H, dd, J = 8.0, 1.0 Hz), 8.96-9.05 (1H, m); 13C NMR (101 MHz, CDCl₃) δ 96.5, 98.8 (b), 117.5, 122.3, 125.0, 125.1, 127.1, 127.3, 127.9, 128.0, 128.6, 128.7, 129.7, 131.9, 133.8, 137.1 (b), 139.8, 142.0, 143.5, 145.9, 146.9, 152.9; 11B NMR (128 MHz, CDCl₃) δ -10.0; FTIR: νmax: 3216 (s), 2262 (w), 2178 (w), 1623 (m), 1597 (m), 1488 (s), 1441 (s), 1195 (m), 986 (m), 919 (m); HRMS (ESI-TOF) m/z [M+H]+ calculated for C₉H₇⁺31BN⁺: 510.2142. Found: 510.2166.

Received: (will be filled in by the editorial staff)
Published online on (will be filled in by the editorial staff)

**Keywords:** cycloaddition - sydnone - alkynylborane - regioselective - pyrazole

[11] CCDC 1453893 contains the supplementary crystallographic data for this compound. This data is provided free of charge by the Cambridge Crystallographic Data Centre.
A Mild and Regiospecific Synthesis of Pyrazoleboranes

Go direct! Alkynylboranes show unprecedented reactivity in their [4 + 2] cycloaddition of sydnones offering access to fully substituted pyrazoles within a few hours at room temperature. This method delivers synthetically valuable pyrazoleboranes with complete control of regioselectivity, and these intermediates can be further elaborated through functionalization of the C-B bond.