Tetrahedron Letters 52 (2011) 1506–1508

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselectivity studies of sydnone cycloaddition reactions of azine-substituted alkynes

Robert S. Foster [a], Harald Jakobi [b], Joseph P. A. Harrity [a,*]

[a] Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK
[b] Bayer CropScience Aktiengesellschaft, BCS AG-R-DIS, 65926 Frankfurt, Germany

ARTICLE INFO

Article history:
Received 9 December 2010
Revised 19 January 2011
Accepted 25 January 2011
Available online 1 February 2011

Keywords:
Sydnones
Cycloadditions
Pyrazoles
Regioselectivity

ABSTRACT

The synthesis of azine-substituted pyrazoles by a sydnone cycloaddition strategy is described. Incorporation of a 3-pyridyl moiety at the sydnone *N*-atom has little effect on either reactivity or regioselectivity, however, 2-ethynyl-pyridine and -pyrimidine undergo cycloaddition with surprisingly poor levels of regiocontrol. A rationale for the observed regiochemical trends and potential routes for improving selectivities are discussed.

Azine-substituted pyrazoles represent a common and versatile class of heteroaromatic systems in organic chemistry. They have been investigated for their biological properties both with respect to the development of agrochemicals[1] and therapeutic agents.[2] Moreover, they are a common class of ligands for the preparation of self-assembling co-ordination networks.[3] Some examples are illustrated in Figure 1. The cycloaddition reaction of alkynes with sydnones provides a convenient and direct method for accessing highly substituted pyrazoles,[4] although this route has not been extensively studied in connection with generating azine-substituted pyrazoles.[5] Nonetheless, we anticipated that sydnone cycloadditions would provide an attractive method for the synthesis of a range of pyrazoles bearing *N*-heteroaromatic substituents, and report herein our findings.

A very narrow range of *N*-azine-substituted sydnones have been reported in the literature, and these have been based on *N*-2-pyridyl **1**[6] and *N*-3-pyridyl **2**[7] substituted analogues (Fig. 2). In our hands, we were readily able to prepare the latter sydnone, however, we were unable to generate the 2-pyridyl isomer **1**. Our experience mirrors that of Ohta et al. who reported difficulties in promoting the *N*-nitrosation step.[6b] Nonetheless, the literature procedure provided sufficient quantities of **2** to be made available and allowed us to study the suitability of this sydnone for *N*-pyridylpyrazole formation. In this regard, recent studies in our laboratories have focused on the cycloaddition of sydnones with alkynylboronates for the synthesis of pyrazole boronic acid deriv-

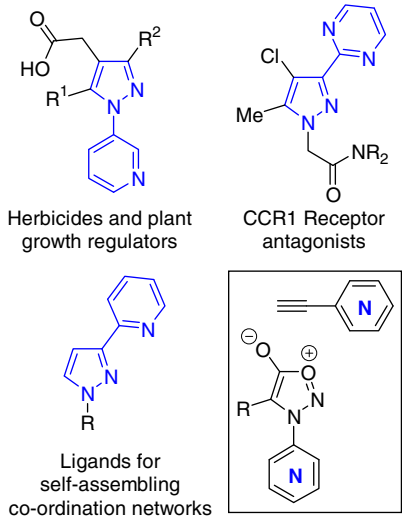


Figure 1.

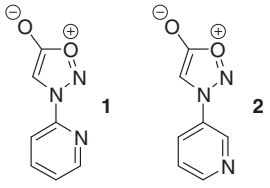
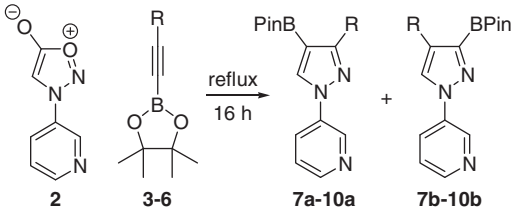


Figure 2.

* Corresponding author. Tel.: +44 114 222 9496; fax: +44 114 222 9346.
E-mail address: j.harrity@shef.ac.uk (J.P.A. Harrity).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.115

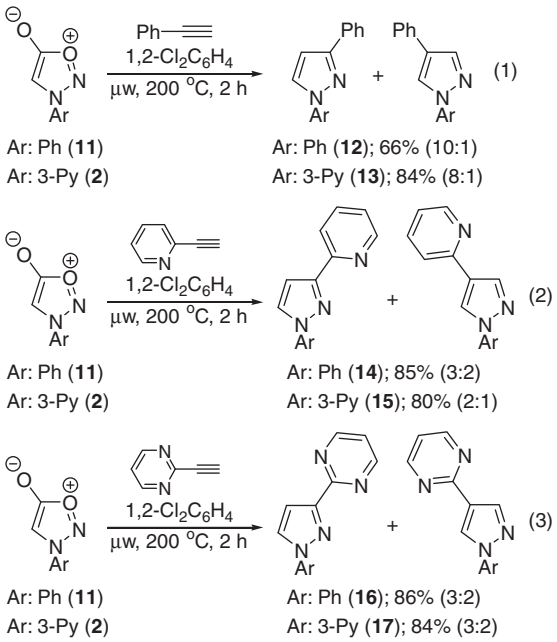
Table 1



Entry	R	Solvent	Yield (**a:b**)
1	Ph; **3**	Xylenes	**7**; 60% (>98:2)
2	Me_3Si; **4**	Xylenes	**8**; 70% (1.3:1)
3	Bu^n; **5**	Mesitylene	**9**; 56% (2.5:1)
4	H; **6**	Mesitylene	**10**; 84% (1:8)

atives,[8] largely because of the associated versatility of the boronate motif.[9] Accordingly, we investigated the potential of this strategy for the synthesis of *N*-azine-substituted pyrazole boronic esters and our results are highlighted in Table 1. The cycloaddition of **2** with a selection of alkynylboronates proved to be successful, providing the corresponding pyrazoles **7–10** in moderate to high yield. The reactions were generally found to be regioselective for the 4-boronate isomer (entries 1–3), with the exception of the terminal alkyne which gave high selectivity for the 3-boronate (entry 4). The selectivities in all cases mirrored those observed for *N*-phenyl derived sydnones (as well as substituted phenyl derivatives), providing further evidence that the sydnone *N*-moiety has little effect on the reaction regiocontrol.[8]

We next turned to the investigation of the cycloadditions of azine-substituted alkynes with sydnones to demonstrate their potential for the synthesis of 3- and/or 4-substituted pyrazoles (Scheme 1). The cycloaddition of phenylacetylene with sydnones **11** and **2** proceeded in good yield and with high levels of regiocontrol for the 3-phenylpyrazole isomers of **12** and **13**, respectively [Eq. 1]. Upon extending this chemistry to 2-ethynylpyridine, we found that the reactions again proceeded efficiently, but with surprisingly lower levels of regiocontrol [Eq. 2]. Finally, we employed 2-ethynylpyrimidine in these cycloaddition reactions and once again found this process to deliver an almost equal mixture of 3- and 4-azine-substituted pyrazoles [Eq. 3].[10]

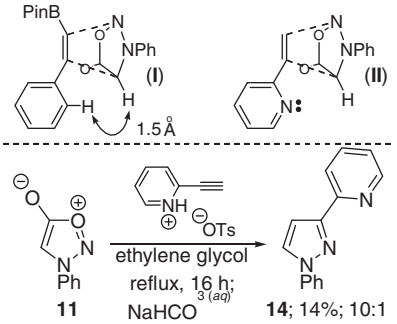


Scheme 1.

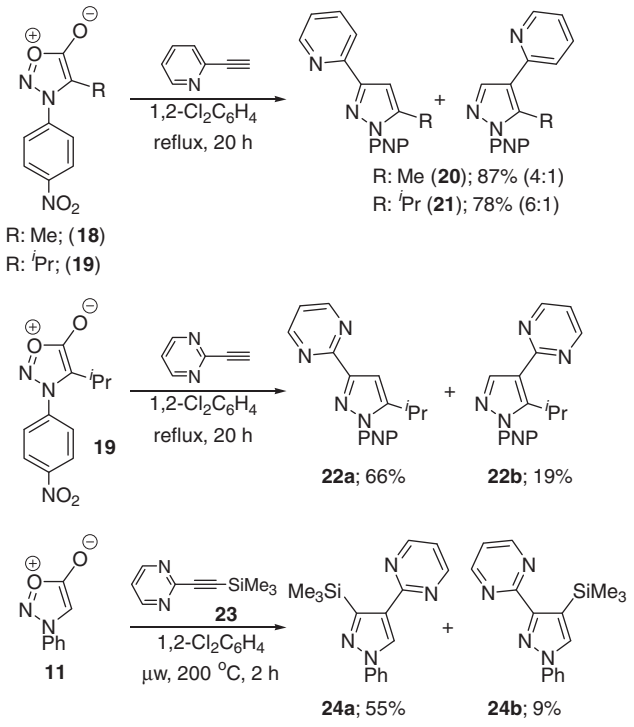
Our earlier work on DFT investigations of the cycloaddition of sydnones and alkynylboronates[8b] allows us to put forward an explanation for the contrasting regioselectivities observed in the cycloadditions of phenylacetylene and 2-ethynyl-pyridine and -pyrimidine (Scheme 2). Specifically, ab initio studies suggest that arylacetylenic boronates prefer to react via the orbital that is perpendicular to the aromatic π-system, accordingly, the transition state leading to the minor 4-arylpyrazole regioisomer is disfavoured by destabilizing steric interactions between the *ortho*-aryl proton and the sydnone C4 H-atom (**I**). Assuming a similar transition state for the cycloaddition of simple arylacetylenes, this model accounts for the high levels of regiocontrol in the formation of 3-phenylpyrazoles **12** and **13**. Moreover, as azineacetylenes can avoid such an interaction (**II**), one would expect a smaller difference in the activation energies of the two competing regiochemical modes. In order to gather some evidence for this, we prepared a 2-ethynylpyridinium salt that we envisaged would be isosteric with phenylacetylene. Indeed, the cycloaddition of this alkyne with **11** proceeded with high levels of regioselectivity, albeit in low yield.[11,12]

These studies raised the question as to whether or not useful levels of regiocontrol could be observed in the cycloaddition reactions of sydnones with azine-substituted alkynes. In this context, we have shown that the incorporation of substituents at the sydnone C4-position, together with the incorporation of a *p*-nitrophenyl group at nitrogen results in optimal yields and regioselectivities in alkyne cycloaddition reactions.[8a,8b,13] Therefore, we decided to employ sydnones **18** and **19** in the cycloaddition of 2-ethynyl-pyridine and -pyrimidine to establish whether more synthetically useful levels of regiocontrol could be achieved, our results are highlighted in Scheme 3. Pleasingly, heating an *o*-dichlorobenzene solution of 2-ethynylpyridine with sydnones **18** and **19** provided the corresponding pyrazoles **20** and **21** in high yield and with useful levels of regiocontrol. Moreover, this trend could be extended to 2-ethynylpyrimidine, providing the pyrazole **22** in high yield as a 7:2 mixture of regioisomers. Finally, we could exploit the apparent low steric volume of the azine ring to carry out a regioselective cycloaddition of unsymmetrical disubstituted alkyne **23**. In the event, pyrazoles **24a,b** were generated in high yield and with good selectivity for **24a**.

In conclusion, we have demonstrated that alkyne/sydnone cycloaddition reactions provide a direct and convenient method to prepare a range of azine-substituted pyrazoles.[14,15] These studies also provide further evidence that the high regioselectivities observed in the reactions of arylalkynes originate from a preferred trajectory of addition where the aryl ring lies perpendicular to the plane of the sydnone.



Scheme 2.



Scheme 3. PNP = 4-$O_2NC_6H_4$.

Acknowledgements

We are grateful to Bayer CropScience and the University of Sheffield for financial support.

References and notes

1. (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467; (b) Jakobi, H.; Ort, O.; Hills, M.; Kehne, H.; Rosinger, C.; Feucht, D. WO2008080504; *Chem. Abstr.* **2008**, *149*, 121249.; (c) Jakobi, H.; Martelletti, A.; Tiebes, J.; Dittgen, J.; Feucht, D.; Haeuser-Hahn, I.; Kehne, H.; Rosinger, C. H. WO 2009152995, 2009; *Chem. Abstr.* **2009**, *152*, 57307.
2. Zhang, P.; Pennell, A. M. K.; Chen, W.; Greenman, K. L.; Sullivan, E. J.; Li, L. WO 2007044885; *Chem. Abstr.* **2007**, *146*, 421980.
3. Fenton, H.; Tidmarsh, I. S.; Ward, M. D. *Dalton Trans.* **2010**, *39*, 3805.
4. Browne, D. L.; Harrity, J. P. A. *Tetrahedron* **2010**, *66*, 553.
5. Huisgen, R.; Gotthardt, H.; Grashey, R. *Chem. Ber.* **1968**, *101*, 536.
6. (a) Chadra, T.; Bhati, S. K.; Yadav, P.; Agarwal, R. C.; Agarwal, T. P.; Kumar, A. *Orient. J. Chem.* **2008**, *24*, 229; (b) Ohta, M.; Masaki, M. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1392.
7. Tien, J. M.; Hunsberger, I. M. *J. Am. Chem. Soc.* **1955**, *77*, 6604.
8. (a) Browne, D. L.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8656; (b) Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7762; (c) Foster, R. S.; Huang, J.; Vivat, J. F.; Browne, D. L.; Harrity, J. P. A. *Org. Biomol. Chem.* **2009**, *7*, 4052.
9. *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.
10. The reactions were run under microwave irradiation for convenience; however, reactions conducted in refluxing xylenes over 16 h gave similar yields and identical regioisomer ratios.
11. Sydnones are known to be acid sensitive, and as **11** was completely consumed in this reaction, we attribute the low yield to the decomposition of this compound.
12. Subjecting a 2:1 mixture of pyrazole regioisomers **14** to TsOH in refluxing ethylene glycol over 16 h did not result in a change of regioisomer ratios. This experiment confirms that the selectivity observed in the cycloaddition of ethynylpyridinium and **11** is not the result of selective decomposition of a 3-substituted pyrazole isomer.
13. Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2010**, *75*, 984.
14. Cycloaddition regioselectivities were estimated using ^{1}H NMR spectroscopy and GC–MS techniques. Regiochemical assignments were made on the basis of diagnostic ^{1}H NMR shift patterns,[8,13] and confirmed in the case of compound **24** by NOE spectroscopy. Regiosiomer ratios were estimated on crude reaction mixtures and confirmed by chromatographic separation in the case of compounds **12**, **16**, **17**, **22** and **24**.
15. *Representative experimental procedure and spectroscopic data for **14**:* A solution of *N*-phenylsydnone (**11**) (81 mg, 0.5 mmol) and 2-pyridylacetylene (103 mg, 1 mmol) in *o*-dichlorobenzene was added to a microwave vial. The vial was sealed and placed in a CEM Discover SP Microwave Reactor and heated at 200 °C for 2 h, before the volatiles were removed in vacuo. Compound **14** was purified by column chromatography on silica gel (30:70 EtOAc/petroleum ether) and the product isolated as a brown solid (94 mg, 85%; 3:2 regioisomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69–8.67 (m, 0.6H), 8.63–8.61 (m, 0.4H), 8.55 (s, 0.4H), 8.21 (s, 0.4H), 8.16–8.14 (m, 0.6H), 8.01 (d, J = 2.5 Hz., 0.6H), 7.82–7.69 (m, 3H), 7.58–7.56 (m, 0.4H), 7.52–7.48 (m, 2H), 7.36–7.31 (m, 1H), 7.26–7.24 (m, 0.6H), 7.19–7.15 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 153.2, 152.0, 151.4, 149.7, 149.4, 140.2, 139.9, 139.2, 136.8, 136.6, 129.5, 129.4, 129.0, 128.3, 126.8, 126.6, 125.3, 122.7, 121.5, 120.3, 119.8, 119.3, 119.2, 106.5; FTIR: 3050 (w), 2919 (w), 1741 (w), 1594 (s), 1567 (w), 1503 (s), 1459 (m), 1412 (m), 1370 (m), 1267 (m), 1050 (w), 962 (m), 756 (s) cm^{-1}; HRMS: m/z $[M+H]^+$ calcd for $C_{14}H_{12}N_3$: 222.1031, found: 222.1031.