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Synthesis and cycloaddition chemistry of oxetanyl-substituted sydnones

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ABSTRACT

Oxetan-3-one reacts with 4-metallated sydnones to provide functionalised precursors to a variety of novel pyrazoles. Intermolecular cycloadditions were found to proceed in variable yield, but intramolecular cycloadditions were very efficient and provide an effective means to generate spiro-substituted heterocyclic intermediates. The potential of these compounds for further elaboration has been highlighted by cross-coupling reactions.

Oxetanes have recently received significant interest as structural units in biologically active molecules as they lend favourable pharmacological properties whilst contributing little to overall molecular weight.[1] The growing interest in these compounds has prompted the development of efficient synthetic routes for the incorporation of oxetanes into a range of molecules.[2] In particular, Carreira, Rogers–Evans and Müller have reported a series of functionalised oxetane cores that are easily elaborated to a diverse range of structures through C–C/C–X bond forming reactions.

Studies in our laboratories have focused on alkyne cycloaddition reactions for the synthesis of small molecule scaffolds through the use of a selection of dienes and dipolar reagents.[3] We have been particularly drawn to the chemistry of sydnones,[4] and have found this class of mesoionic reagents to be especially effective for the synthesis of a diverse range of pyrazoles.[5] We were intrigued by the notion of merging sydnone and oxetane chemistry as we envisaged that it could provide a flexible approach to a variety of useful heteroaromatic scaffolds by offering the opportunity to elaborate the mesoionic intermediate via alkylation or cycloaddition reactions (Fig. 1). We report herein the successful realisation of this idea and the scope and limitations of this chemistry as a method for delivering oxetane-substituted pyrazoles.

We began our studies by developing a convenient and general approach to oxetane-substituted sydnones. Specifically, we opted to take advantage of the ready deprotonation of these mesoionic reagents to form an organometallic intermediate[6] that could be added to commercially available oxetan-3-one. As highlighted in Scheme 1, the low temperature deprotonation of sydnones **1a–c** with MeMgBr followed by addition of oxetan-3-one proved to offer a convenient access to a small selection of sydnones **2a–c** in acceptable overall yield. The compounds were found to be unstable to chromatography on silica gel, but were routinely isolated by trituration from EtOH.

With an effective means of generating oxetane-substituted sydnones in hand, we wanted to explore the use of these dipolar reagents in cycloadditions with a selection of commercially available alkynes.[7] Our results are summarised in Table 1. Microwave-promoted cycloaddition of **2a** with electron deficient alkynes proceeded rapidly to provide the corresponding products in high

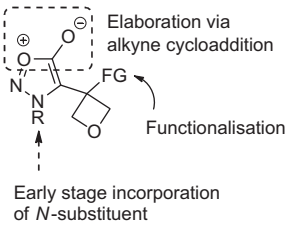
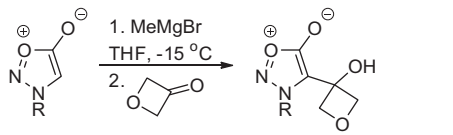


Figure 1. Design of oxetanyl-substituted sydnones



R:Ph; **1a**
R:4-MeOC$_6$H$_4$; **1b**
R:Bn; **1c**

R:Ph; **2a;** 69%
R:R:4-MeOC$_6$H$_4$; **2b;** 63%
R:Bn; **2c;** 54%

Scheme 1. Synthesis of oxetanyl-substituted sydnones

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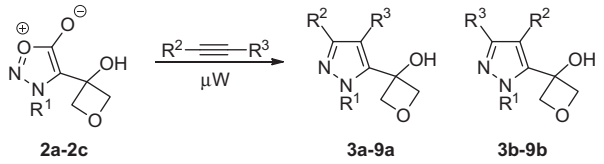
Table 1
Intermolecular sydnone cycloadditions

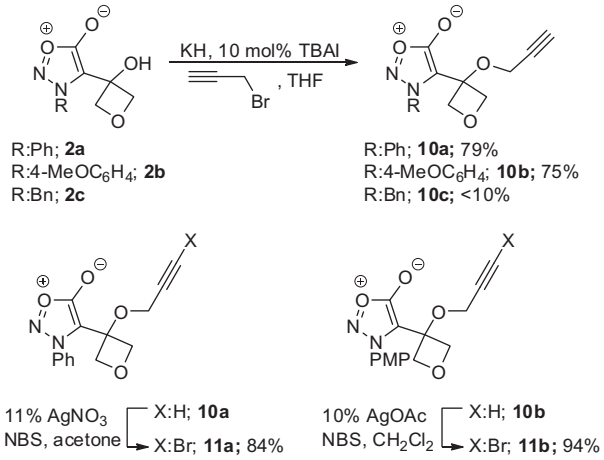


Entry	R^1	R^2	R^3	Time	Yield (**a**:**b**)[d]
1	Ph; **2a**	CO_2Me	CO_2Me	5 min[b]	**3**; 92%
2	Ph; **2a**	CO_2Et	H	30 min[c]	**4**; 66% (7:1)
3	Ph; **2a**	Ph	H	6 h[c]	**5**; 51% (>98:2)
4	Ph; **2a**	Me_3Si	H	3.5 h[c]	**6**; 17% (>98:2)
5	PMP; **2b**[a]	CO_2Me	CO_2Me	20 min[b]	**7**; 60%
6	PMP; **2b**[a]	CO_2Et	H	1 h[c]	**8**; 44% (5:1)
7	Bn; **2c**	CO_2Et	H	30 min[b]	**9**; 21% (2:1)

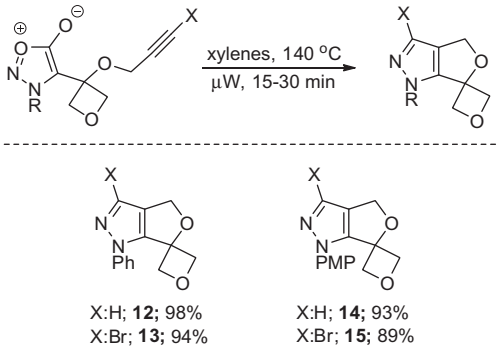
[a] PMP: 4-$MeOC_6H_4$.
[b] Reaction conducted in 1,2-$Cl_2C_6H_4$ at 180 °C.
[c] Reaction conducted in xylenes at 140 °C.
[d] Regioselectivities determined by 400 MHz ^{1}H NMR spectroscopy.

yield, and with good regiocontrol in the case of **4a** (entries 1 and 2). In contrast, phenyl- and trimethylsilyl-acetylene were found to be rather sluggish and afforded the products in significantly lower yield, but with excellent regioselectivity for isomer **a** in each case (entries 3 and 4). PMP-substituted sydnone **2b** was found to be less reactive than **2a** and afforded products in reduced yield (entries 5 and 6), however, Bn-substituted sydnone **2c** proved to be significantly less effective in cycloaddition reactions and appeared to undergo substantial decomposition returning poor yields of pyrazole products (entry 7).

As only a narrow set of substrates participated adequately in the key cycloaddition step, we decided to explore the potential of an intramolecular variant in the hope that improved yields could be realised. Accordingly, we subjected sydnones **2a**–**c** to propargylation reactions and our results are shown in Scheme 2. In the event, sydnones **2a,b** underwent a smooth base-mediated addition to propargyl bromide to give alkynes **10a** and **10b** in good yield. Once again however, we found Bn-substituted sydnone **2c** to be unstable and the corresponding alkyne **10c** could only be isolated in very low yield from a complex mixture. The instability of 4-substituted Bn-sydnone **2c** in comparison to the *N*-aryl analogues is notable and is in line with similar observations made by Padwa and co-workers.[8] Nonetheless, with efficient routes to **10a**,**b** in hand, and looking ahead to the formation of functionalised



Scheme 2. Synthesis of substrates for intramolecular cycloaddition

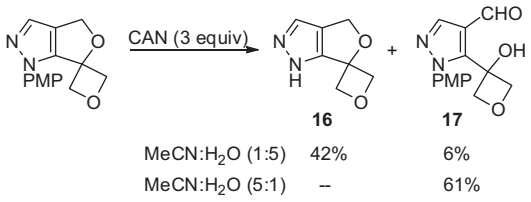


Scheme 3. Intramolecular sydnone cycloadditions

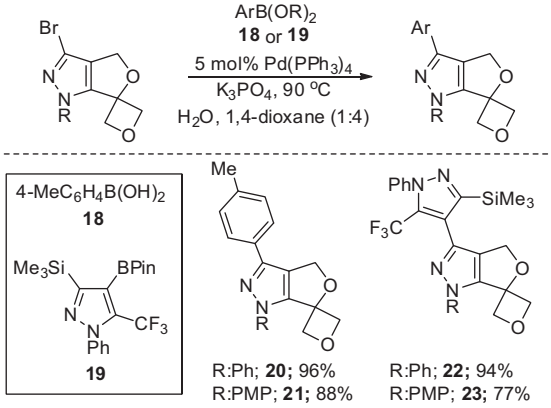
pyrazole products, we decided to carry out the conversion of these substrates into the corresponding bromoalkynes. We were pleased to find that this chemistry proceeded quite efficiently to give sydnones **11a,b** in high yields.

In studying the intramolecular cycloaddition of alkynes **10a,b** and **11a,b**, we opted to employ microwave irradiation so as to be able to make a direct comparison with the reactions shown in Table 1. Pleasingly, we found that all substrates formed the corresponding pyrazoles **12**–**14** in excellent yield and within a short reaction time (Scheme 3).

The spiro-oxetane intermediates **14** and **15** represent interesting fragments for drug discovery as they have a low molecular weight, low *clog P* and nonplanar polar moiety.[9] In order to employ these pyrazoles as fragments however, we recognized the need to remove the PMP-group to access the free pyrazole. We therefore investigated the CAN deprotection of **14** and our results are shown in Scheme 4. The deprotection reaction was surprisingly challenging and provided an unexpected by-product **17** that appears to derive from oxidation and hydrolysis of the 5-membered heterocycle ring. The product distribution was found to be dependent on water concentration, and after significant optimisation we were able to uncover conditions for the selective synthesis of both pyrazoles, albeit in modest yield.



Scheme 4. CAN oxidation of 14



Scheme 5. Cross-coupling reactions

In addition, we envisaged that 3-bromopyrazoles **13** and **15** would provide a convenient means for conducting Suzuki cross-coupling reactions. We employed boronic acid **18** and more heavily substituted pinacol ester **19**[10] to highlight the scope of this chemistry. Pleasingly, both substrates underwent clean and high yielding coupling to provide the corresponding biaryl products (Scheme 5).

In conclusion, we have shown that oxetane-substituted sydnones offer an effective vehicle for generating a range of pyrazole intermediates via alkyne cycloaddition processes. In particular, the intramolecular cycloaddition provides an efficient means of generating spiro-fused intermediates that have the potential for exploitation as low molecular weight polar fragments in lead discovery.[11]

Acknowledgments

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References and notes

1. (a) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7736; (b) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Marki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4512; (c) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227.
2. (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052; (b) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780; (c) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259.
3. (a) Moore, J. E.; Goodenough, K. M.; Spinks, D.; Harrity, J. P. A. *Synlett* **2002**, 2071; (b) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707; (c) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3889; (d) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860; (e) Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.* **2006**, 3323; (f) Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *J. Am. Chem. Soc.* **2007**, *129*, 2691; (g) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866; (h) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893; (i) Auvinet, A.-L.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2769.
4. (a) Stewart, F. H. C. *Chem. Rev.* **1964**, *64*, 129; (b) Browne, D. L.; Harrity, J. P. A. *Tetrahedron* **2010**, *66*, 553.
5. (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; (d) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396; (e) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2010**, *75*, 984.
6. Tien, H.-J.; Fang, G.-M.; Lin, S.-T.; Tien, L.-L. *J. Chin. Chem. Soc.* **1992**, *39*, 107.
7. (a) Huisgen, R.; Grashley, R.; Gotthardt, H.; Schmidt, R. *Angew. Chem. Int. Ed.* **1962**, *1*, 48; (b) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234; (c) Delauney, T.; Geux, P.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Org. Lett.* **2010**, *12*, 3328; (d) Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 8840.
8. Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786.
9. The low molecular weight and lipophilicity of compound **16** offers the opportunity to incorporate a range of fragments for lead discovery (estimated $\mathrm{clog}P = -1.3$; ChemBioDraw Ultra™ version 12.0 Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114.
10. Foster, R. S.; Jakobi, H.; Harrity, J. P. A. *Org. Lett.* **2012**, *14*, 4858.
11. *General procedure for the synthesis of 4-(3-hydroxyoxetan-3-yl)-N-substituted-sydnones **2**:* A 3 M solution of methyl magnesium bromide in hexane (1.1 equiv) was added dropwise to a solution of sydnone **1** (1 equiv) in anhydrous THF at −15 °C. After stirring at this temperature for 1 h 3-oxetanone (1.1 equiv) was added and the resulting mixture was allowed to warm to room temperature, and left to stir for 5 h. The mixture was quenched by addition of a saturated aqueous solution of NH_4Cl, and the volatiles were removed in vacuo. The residue was extracted with CH_2Cl_2 and the combined organic fractions were dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was then triturated with EtOH and the product collected by filtration to afford the title compound **2**. *4-(3-Hydroxyoxetan-3-yl)-3-phenyl-3H-1,2,3-oxadiazol-1-ium-5-olate* (**2a**): Following the general procedure using *N*-phenylsydnone (**1a**) (1.00 g, 6.17 mmol) in THF (10 mL), the product **2a** was isolated as a yellow solid (1.01 g, 69%). Mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H, Ar*H*), 7.76–7.70 (m, 1H, Ar*H*), 7.69–7.63 (m, 2H, Ar*H*), 4.90 (s, 1H, O*H*), 4.75 (d, J = 7.5 Hz, 2H, CH_2), 4.61 (d, J = 7.5 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 134.4, 132.9, 130.2, 124.1, 108.5, 80.6, 67.8; FTIR: 3289 (br), 2950 (w), 2882 (w), 1721 (s), 1476 (m), 1267 (m), 1187 (m), 1140 (w), 1156 (w), 1018 (m), 982 (m), 773 (m), 690 (m); HRMS: m/z $[MH]^+$ calcd for $C_{11}H_{11}N_2O_4$: 235.0719, found: 235.0709. *4-(3-Hydroxyoxetan-3-yl)-3-(4-methoxyphenyl)-3H-1,2,3-oxadiazol-1-ium-5-olate* (**2b**): Following the general procedure with *N*-*p*-methoxyphenylsydnone (**1b**) (2.07 g, 10.75 mmol) in THF (20 mL), the product **2b** was isolated as a beige solid (1.80 g, 63%). Mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 9.0 Hz, 2H, Ar*H*), 7.10 (d, J = 9.0 Hz, 2H, Ar*H*), 4.86 (s, 1H, O*H*), 4.77 (d, J = 7.5 Hz, 2H, CH_2), 4.62 (d, J = 7.5 Hz, 2H, CH_2), 3.93 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.7, 127.0, 125.5, 115.2, 108.3, 80.7, 67.8, 55.8; FTIR: 3343 (m), 2878 (w), 1721 (s), 1606 (m), 1512 (s), 1469 (m), 1306 (w), 1256 (s), 1173 (m), 1115 (w), 1021 (m), 982 (m), 837 (m); HRMS: m/z $[MH]^+$ calcd for $C_{12}H_{13}N_2O_5$: 265.0824, found: 265.0819. *3-Benzyl-4-(3-hydroxyoxetan-3-yl)-3H-1,2,3-oxadiazol-1-ium-5-olate* (**2c**): Following the general procedure with *N*-benzylsydnone (**1c**) (0.300 g, 1.70 mmol) in THF (5 mL), the product **2c** was isolated as a beige solid (0.228 g, 54%). Mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.37 (m, 3H, Ar*H*), 7.33 (d, J = 3.5 Hz, 2H, Ar*H*), 5.60 (s, 2H, CH_2), 4.93–4.63 (m, 3H, CH_2 and O*H*), 4.40 (d, J = 6.0 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 130.4, 130.0, 129.4, 128.2, 106.1, 80.8, 69.2, 56.5; FTIR: 3317 (m), 2955 (w), 2881 (w), 1724 (s), 1495 (m), 1456 (m), 1328 (w), 1185 (m), 980 (m), 868 (w), 737 (m), 700 (m); HRMS: m/z $[MH]^+$ calcd for $C_{12}H_{13}N_2O_4$:249.0864, found: 249.0875.