A novel approach to functionalised pyridazinone arrays†

Matthew D. Helm,[a] Andrew Plant[b] and Joseph P. A. Harrity*[a]

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A series of 3,6-dichloro-1*H*-pyridazin-4-ones have been prepared *via* the cycloaddition of 3,6-dichlorotetrazine with alkynylboronates, and their employment as useful synthetic intermediates was highlighted through a selection of highly regioselective C–O, C–S and C–C bond forming reactions.

Pyridazinones represent an important class of bioactive compounds, and they have been particularly widely exploited as crop protection agents and as pharmaceuticals.[1] For example, the analgesic anti-inflammatory agent emorfazone **1**[2] and the herbicide norflurazon **2**[3] are founded on this motif, whilst Stevenson and coworkers found that the structurally related **3** also showed good herbicidal activity (Chart 1).[4] Recent work in our labs has uncovered an efficient route to pyridazines that we felt would be amenable to the preparation of a range of pyridazinone scaffolds that would represent useful intermediates in agrochemical discovery research. Specifically, we hoped to prepare a series of heterocycles **4** that would allow flexible introduction of functionality around the ring and that provided a functional group at C-6 for late stage modification. We report herein a flexible route to this motif and some representative functionalisation reactions of the C–Cl bond.

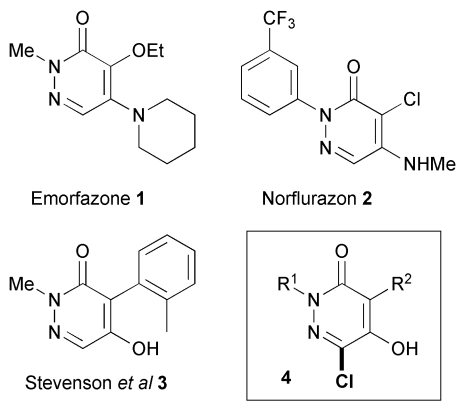
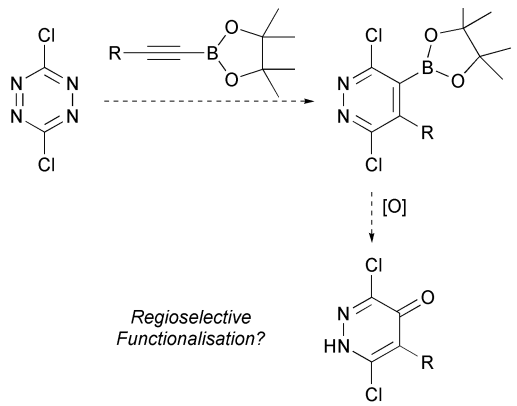


Chart 1 Representative bioactive pyridazinones.

The synthesis of pyridazines is most commonly carried out by condensation of hydrazine with an appropriately functionalized dicarbonyl compound (or equivalent).[1] This approach can be rather limited if more heavily functionalised heterocycles are required because the starting substrate may be inaccessible or may contain incompatible functionality. An alternative route that allows heavily functionalised pyridazines to be readily accessed is through the Carboni–Lindsey cycloaddition reaction.[5] In this context we have shown that highly functionalised pyridazine boronic esters can be accessed by the cycloaddition of tetrazines with alkynylboronates.[6,7] Additionally, and in the context of this study, we further demonstrated that these intermediates could be elaborated to pyridazinones by oxidation, albeit in a single example. In an effort to broaden this technique to include pyridazinone scaffolds, we envisaged that the cycloaddition of alkynylboronates with dichlorotetrazine would provide a pyridazine boronic ester that could be elaborated to a pyridazinone with the option of functionalising at C-3 or C-6. Notably, a crucial goal in this study was the realisation of conditions that would allow a number of groups to be incorporated into these intermediates with high levels of regiocontrol (Scheme 1).



Scheme 1 Alkynylboronate cycloaddition route to pyridazinones.

We began our studies by investigating the cycloaddition reaction of 3,6-dichlorotetrazine **5**[8,9] with a representative series of alkynylboronates. Pleasingly, this technique delivered the key 2,6-dichloropyridazines **6** in good yield in all cases examined. We found that the reaction proceeded most efficiently in xylenes; running the reaction at similar temperatures in non-refluxing solvent gave lower yields due to sublimation of the volatile tetrazine from the reaction medium. Furthermore, oxidation of substrates **6b–d** proceeded rapidly to provide the corresponding pyridazinones **7** in good yield within a short reaction time (Scheme 2).

With the pyridazinones in hand, we turned our attention to the regioselective functionalisation reactions (Scheme 3).[10] Preliminary attempts to add oxygen based nucleophiles invariably led only to recovery of the starting compound. We surmised that this poor reactivity was probably due to the generation of an electron rich pyridazin-4-olate *via* deprotonation of the

[a]*Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK S3 7HF. E-mail: j.harrity@sheffield.ac.uk; Fax: +44 (0114) 222 9346; Tel: +44 (0114) 222 9496*
[b]*Research Chemistry, Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, UK RG42 6EY*

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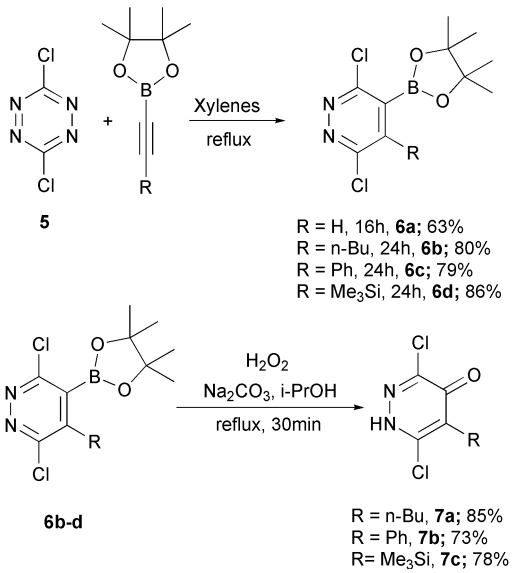
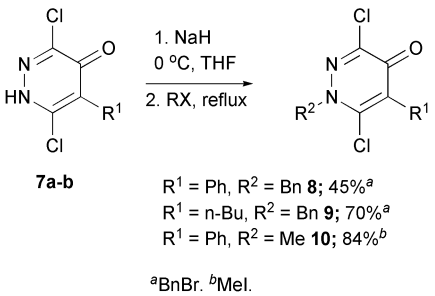


5 6b-d

Scheme 2 Synthesis of 3,6-dichloro-1*H*-pyridazin-4-ones.



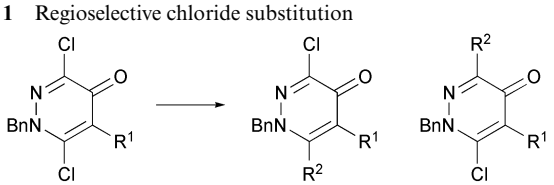
7a-b

Scheme 3 Pyridazinone protection.

acidic NH. Accordingly we carried out the *N*-protection of these substrates and found that both methylation and benzylation proceeded in modest to excellent yield.

Substitution of the *N*-protected substrates **8** and **9** were next investigated and the results are outlined in Table 1. Substitution of chloride for phenoxide was found to take place in good yield and with complete regiocontrol for addition at C-6 to give

Table 1 Regioselective chloride substitution

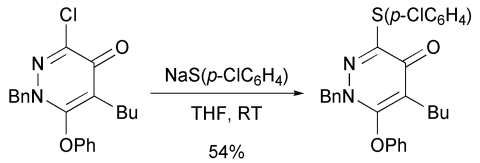


8-9 11a-14a 11b-14b

Entry	R^1	Conditions	R^2	Yield
1	Ph **8**	NaOPh, THF, 40 °C	OPh	**11a**; 77%[a]
2	Bu **9**	NaOPh, THF, 40 °C	OPh	**12a**; 70%[b]
3	Bu **9**	NaS(*p*-ClC_6H_4), THF, RT	S(*p*-ClC_6H_4)	**13a**; 96%
4	Bu **9**	$PhB(OH)_2$, 3% $Pd(PPh_3)_4$, Na_2CO_3, tol., reflux	Ph	**14b**; 62%

[a] 16% of *bis*-phenoxide was also isolated. [b] 11% of *bis*-phenoxide was also isolated.

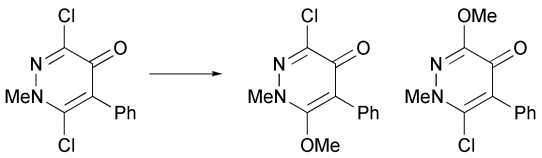
products **11a** and **12a** respectively (entries 1 and 2). Further studies demonstrated that substitution of the chloride at C-6 could also be performed by a base mediated thiolate substitution to give **13a** (entry 3). In contrast however, the Suzuki coupling reaction with phenylboronic acid proceeded with complete reversal of regiochemistry to provide isomer **14b** in 62% yield (entry 4). This divergence in regiochemistry was unexpected but may be due to the greater steric congestion around C-6 in comparison to that at C-3.[11] Finally, the employment of the remaining chloride to introduce further diversity was demonstrated in a single case in this series by the substitution of the C-3 chloride in **12a** by thiolate to give **15** (Scheme 4).



12a 15

Scheme 4 Thiolate substitution at C-3.

With the methodology in hand for the selective functionalisation of the dichloropyridazinones, we set about employing this approach to the synthesis of analogues of the herbicidal core reported by Dupont chemists (**4** in Chart 1).[4] We prepared compound **10** as before, although sequential cycloaddition, oxidation and *N*-methylation without intermediate purification gave this compound in higher overall yield (84% over three steps). We next investigated the chloride substitution of **10** by methoxide and were surprised to find this to be poorly regioselective and to favour displacement of the 3-Cl-substituent.[12] However, modification of the reaction conditions allowed to us once again to achieve a highly regioselective substitution at the C-6 position (Scheme 5).



10	16a	16b
NaOMe, THF, 40 °C	27%	56%
Na_2CO_3, MeOH, reflux	100%	0%

Scheme 5 Methoxide substitution studies.

Finally, Pd-catalysed dechlorination and demethylation provided an analogue of the Stevenson compound **17**. Moreover, the potential exploitation of the chloride in **16a** for further elaboration was demonstrated by Suzuki cross-coupling to provide **18** after demethylation (Scheme 6).

In conclusion, we have developed an efficient route to 3,6-dichloro-1*H*-pyridazin-4-ones and demonstrated that they undergo regioselective C–O, C–S and C–C bond forming reactions.

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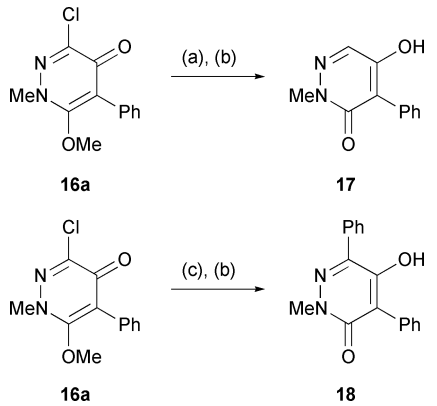

Scheme 6 *Reagents and conditions*: (a) HCO_2NH_4, 5% Pd/C, EtOH; 100%. (b) TMSCl, NaI, MeCN. **17**; 90%. **18**; 100%. (c) $PhB(OH)_2$, 2.5% $Pd(PPh_3)_4$, Na_2CO_3, tol.; 71%.

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8 We have developed a modified route to this compound that avoids the use of chlorine gas. See Supplementary Information† for experimental details.

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11 The regiochemistry of compound **12a** was established by X-ray crystal structure of the debenzylated compound, the regiochemistry of **16a** was therefore based on the assumption that phenoxide addition to **4** followed the same regiochemistry pattern. The regiochemistry of **13a** was established by NOE spectroscopy and that of **14b** was established by X-ray crystal structure after debenzylation and formation of the *O*-4-nitrobenzoate ester. X-Ray crystallography data for debenzylated **12a**: $C_{14}H_{15}ClN_2O_2$, $M = 278.73$, monoclinic, $a = 9.227(2)$, $b = 12.144(3)$, $c = 12.904$ Å, $\beta = 91.550°$, $U = 1445.5(6)$ Å^3, space group $P2(1)/c$, $Z = 4$, $\mu = 0.264$ mm^{-1}, 11 319 reflections measured, 1865 independent reflections, $R1 = 0.0916$ and w$R2 = 0.1266$ for all data. X-Ray crystallography data for *O*-4-nitrobenzoate ester of debenzylated **14b**: $C_{21}H_{18}ClN_3O_4$, $M = 411.83$, tetragonal, $a = 25.7394(10)$, $b = 25.7394(10)$, $c = 5.9168(6)$ Å, $U = 3920.0(5)$ Å^3, space group $P4/n$, $Z = 8$, $\mu = 0.228$ mm^{-1}, 53 474 reflections measured, 2407 independent reflections, $R1 = 0.0801$ and w$R2 = 0.1143$ for all data. CCDC reference numbers 620790 and 620791. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613223e. See Supplementary Information† for NOE spectroscopy of **13a**.

12 The regiochemistry of **16a** was established by NOE spectroscopy, see Supplementary Information† for details.

