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4-Bromomethyl-2-chlorooxazole—a versatile oxazole cross-coupling unit for the synthesis of 2,4-disubstituted oxazoles

Gail L. Young,[a] Stephen A. Smith[b] and Richard J. K. Taylor[a,*]

[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[b]*GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

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Abstract—The synthesis of the novel oxazole building block, 4-bromomethyl-2-chlorooxazole, and its palladium-catalysed cross-coupling reactions to make a range of 2,4-disubstituted oxazoles, is described. Selectivity for the 4-bromomethyl position is observed, with Stille coupling effected in good to excellent yields, or Suzuki coupling in moderate yields, to provide a range of 4-substituted-2-chlorooxazoles. Subsequent coupling at the 2-chloro-position can be achieved through either Stille or Suzuki reactions in excellent yields.

The 2,4-disubstituted oxazole is a motif found in many natural products, which display biological activity over a wide range of therapeutic areas. Examples include virginiamycin M_2[1] (antibiotic), hennoxazole A[2] (antiviral) and leucascandrolide A[3] (cytotoxic and antifungal) (Fig. 1).

The most commonly-used method for the installation of oxazoles in synthesis is through cyclodehydration reactions of peptide derivatives,[4] but these can often prove incompatible with sensitive functionality or require extensive protecting group strategies. Palladium-catalysed coupling for the preparation of substituted oxazoles has also been used but this has been restricted to mono-coupling with further derivatisation required for the synthesis of di-substituted compounds.[5,6]

Due to the limitations of the present methodology, we were keen to explore the possibility of developing a pre-formed oxazole unit, which could be sequentially elaborated under mild palladium-catalysed coupling conditions to provide easy access to a range of 2,4-disubstituted oxazoles. To this end, the novel oxazole, 4-bromomethyl-2-chlorooxazole **5**, has been prepared in good yield (84% over two steps) from the previously reported ethyl 2-chlorooxazole-4-carboxylate **2**[6] through a reduction/bromination strategy (Scheme 1). Oxazole **2** can be synthesised on a 100 g scale in two steps from ethyl bromopyruvate **1**. Reduction of ethyl 2-chlorooxazole-4-carboxylate **2** to 4-hydroxymethyl-2-chlorooxazole **4** with DIBAL-H proceeds in excellent yield following aqueous work-up and further purification is not required. Triphenylphosphine–carbon tetrabromide bromination then proceeds smoothly to provide **5**, which proved stable for periods in excess of 3 months when kept under an inert atmosphere at −20 °C.

Alternative methods for the conversion of ester **2** into alcohol **4** were also explored. Treatment of **2** with sodium borohydride resulted in the formation of a mixture of the desired product **4** together with the over-reduced by-product **6** and competing polymerisation products. Hydrolysis of **2** to the carboxylic acid **3** and subsequent borane reduction to **4** was also investigated. Interestingly, under basic saponification conditions the desired compound **3** was obtained in good yield, whilst under acidic hydrolysis the product isolated was **7**, where efficient displacement of the 2-chloro-moiety with ethanol predominated. Disappointingly, borane reduction of acid **3** only gave a moderate yield of **4** and therefore DIBAL-H reduction remains the preferred method for the preparation of **4**.

With 4-bromomethyl-2-chlorooxazole **5** in hand, we first carried out a proof of principle study to determine the success (and regioselectivity) of the proposed process. Stille coupling[7] of 4-bromomethyl-2-chlorooxazole **5**

Keywords: Oxazole; Palladium; Cross-coupling; Stille; Suzuki.
* Corresponding author. Tel.: +44-0-1904-432606; fax: +44-0-1904-434523; e-mail: rjkt1@york.ac.uk

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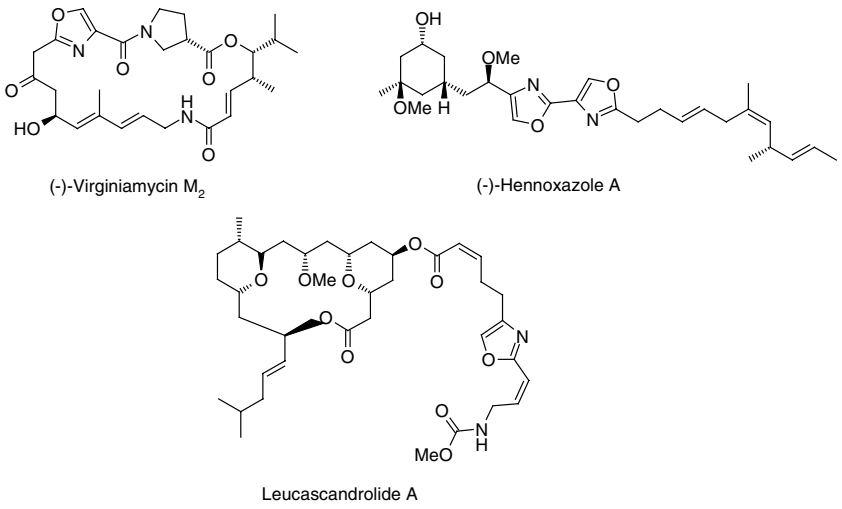
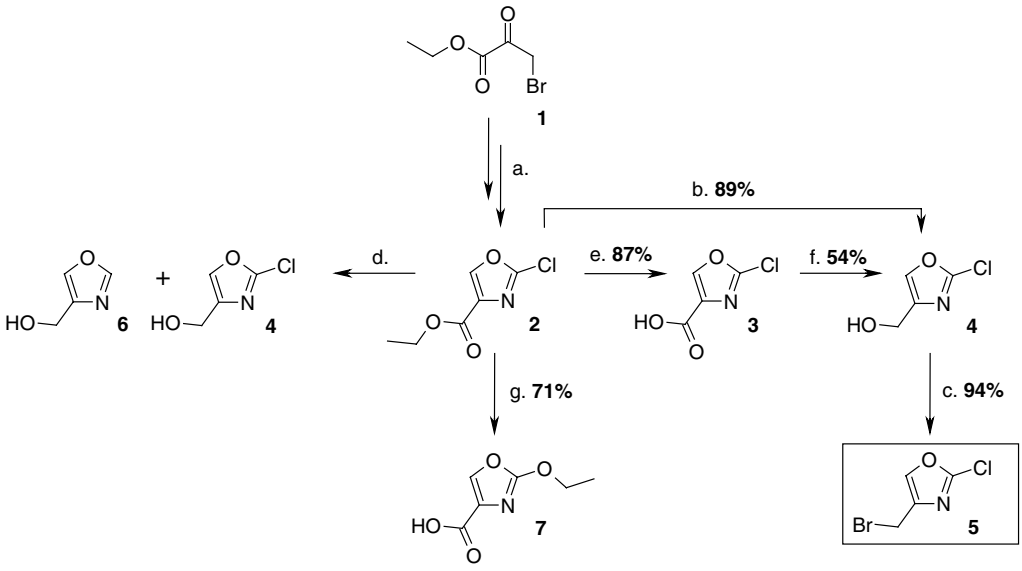


Figure 1. Representative oxazole natural products.

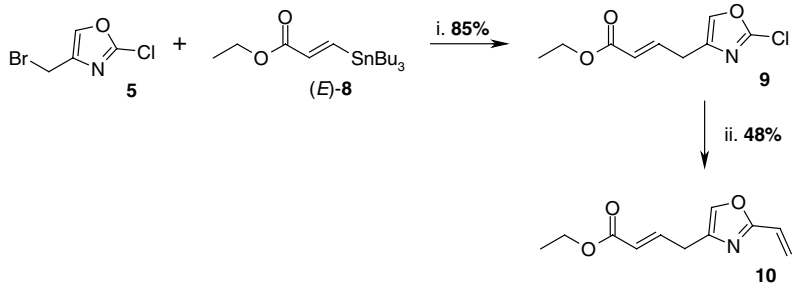


Scheme 1. Synthesis of 4-bromomethyl-2-chlorooxazole **5**. Reagents and conditions: (a) two steps;[6] (b) DIBAL-H, CH_2Cl_2, −78 °C to rt, 89%; (c) CBr_4, PPh_3, 2,6-lutidine, MeCN, 0 °C, 94%; (d) $NaBH_4$, EtOH, rt, 38% of **4**; (e) NaOH (aq), THF, rt, 87%; (f) BH_3, THF, −10 °C–rt, 54%; (g) HCl (aq), 1,4-dioxane, 110 °C, 71%.

with ethyl (*E*)-3-(tributylstannyl)propenoate **8** showed selectivity for the 4-bromomethyl position and subsequent coupling of the isolated product **9** at the 2-chloro-position with tributyl(vinyl)tin also proceeded in reasonable yield to give the novel 2,4-disubstituted oxazole **10** (Scheme 2).

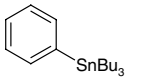
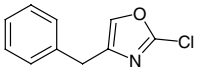
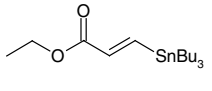
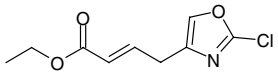
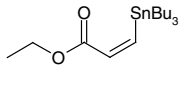
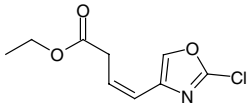
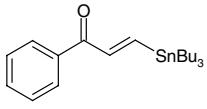
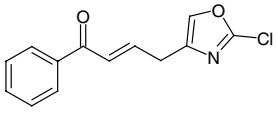
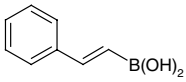
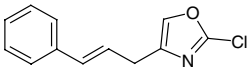
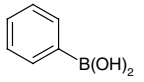
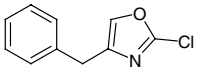
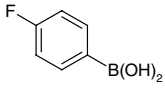
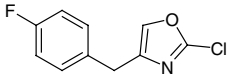
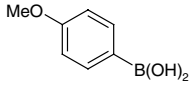
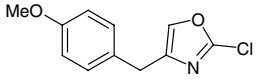
Optimisation of the Stille cross-coupling of **5** was carried out with tributylphenyltin to form 4-benzyl-2-chlorooxazole **11** (Table 1, entry i). Efforts to minimise observed homocoupling of the organostannane[8] provided optimum conditions of $Pd_2(dba)_3$ with added tri-2-furylphosphine (TFP) ligands in dry degassed NMP. With this system, complete selectivity for the 4-bromomethyl position was obtained. $Pd(PPh_3)_4$ and $PdBnCl(PPh_3)_2$ produced mixtures of mono-coupling at the bromide site and the double coupled product whilst $PdCl_2(PPh_3)_2$ showed little or no coupling, even after extended periods at reflux. Studies on Suzuki coupling[9] with *trans*-phenylvinyl boronic acid also identified the $Pd_2(dba)_3$/TFP combination to be optimum using DME as the solvent and Na_2CO_3 as the base (entry v).

Stille and Suzuki reactions were then employed to prepare a variety of 4-substituted-2-chlorooxazoles (Table 1). Stille reactions were generally achieved in good yields using the optimised conditions (entries i and ii) but due to the substrate sensitivity of the reaction, an alternative catalyst can sometimes offer augmented yields (entries iii and iv). Intriguingly, it was observed that when coupling was carried out with (*E*)-**8** (entry ii), the desired coupled product **9** was isolated in good yield, whereas when the *cis*-stannane (*Z*)-**8** (entry iii) was used, coupling proceeded with migration of the double bond into



Scheme 2. Selective Stille coupling of **5**. Reagents and conditions: (i) $Pd_2(dba)_3$, tri-2-furylphosphine (TFP), NMP, 80 °C, 3 h, 85%; (ii) tributyl-(vinyl)tin, $PdCl_2(PPh_3)_2$, 1,4-dioxane, 100 °C, 3 h, 48%.

Table 1. Stille[a] and Suzuki[b] cross-coupling of 4-bromomethyl-2-chlorooxazole **5** to form 4-substituted-2-chlorooxazoles

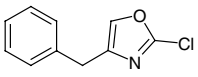
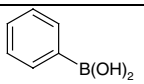
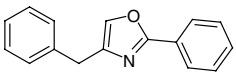
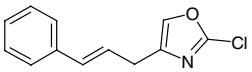
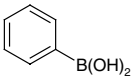
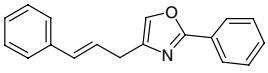
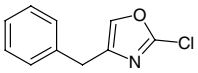
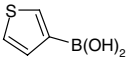
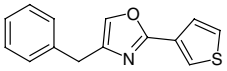
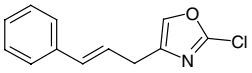
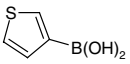
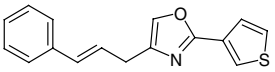
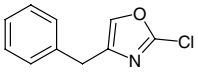
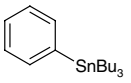
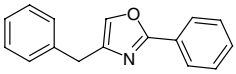
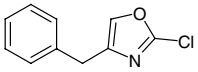
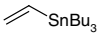
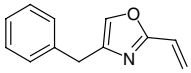
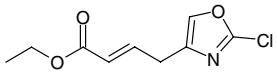
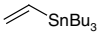
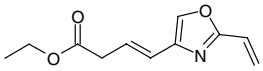
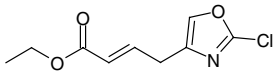
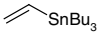
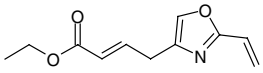
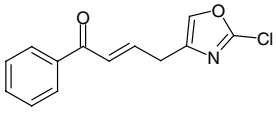
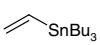
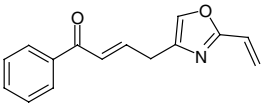
Entry	Organometallic	Product		Isolated yield (%)
i			**11**	58[c]
ii	 (*E*)-**8**		**9**	85
iii	 (*Z*)-**8**		**12**	39 (78)[d]
iv			**13**	76 (84)[e]
v			**14**	67
vi			**11**	34
vii			**15**	35
viii			**16**	44

[a] Stille reaction conditions. **5** (1 equiv), organostannane (1.2 equiv), Pd_2dba_3 (2.5 mol%), TFP (20 mol%), NMP (0.1 M), 80 °C, 1–3 h.
[b] Suzuki reaction conditions. **5** (1 equiv), boronic acid (1.2 equiv), Pd_2dba_3 (2.5 mol%), TFP (20 mol%), Na_2CO_3 (2 M aq, 4 equiv), toluene/EtOH 1:1 (0.1 M), 80 °C, 18 h.
[c] Reaction was carried out at 100 °C.
[d] $\{Pd[C(CO_2Me)]_4(Succ)\}_2(NBu_4)_2$ (5 mol%), THF (0.1 M), 80 °C, 1 h.
[e] $PdBnCl(PPh_3)_2$ (5 mol%), THF (0.1 M), 50 °C, 1 h.

conjugation with the oxazole with retention of the *cis*-geometry to form **12**. The somewhat lower yields obtained in the Suzuki couplings (entries v–viii) are due to reduced selectivity for the 4-bromomethyl position over the 2-chloro-position, resulting in mixtures of mono and di-substituted oxazoles, and competing polymerisation reactions.

Due to the increased reactivity of the chloride moiety in the Suzuki reaction, seen by a much higher proportion of double-coupled product in reactions of **5**, optimisation of coupling at the chloride site was primarily carried out on the Suzuki coupling of **11** with phenylboronic acid to form **17** (Table 2, entry i). These studies identified the preferred system as catalytic $PdCl_2(PPh_3)_2$ with DME as the solvent and Na_2CO_3 as the base. $PdBnCl(PPh_3)_2$ also gave reasonable yields with DME and Na_2CO_3 (58%) and $Pd(PPh_3)_4$ provided the coupled product **17** in a moderate yield (32%). $PdCl_2(PPh_3)_2$ also proved to be optimum for Stille coupling at the 2-chloro-moiety using DMF or 1,4-dioxane as the solvent. It must be noted that all couplings at the 2-chloro

Table 2. Suzuki[a] and Stille[b] cross-coupling of 4-substituted-2-chlorooxazoles to form 2,4-disubstituted oxazoles

Entry	Oxazole chloride		Organometallic	Product		Isolated yield (%)
i		**11**			**17**	97
ii		**14**			**18**	81
iii		**11**			**19**	60 (82)[c]
iv		**14**			**20**	67
v		**11**			**17**	96
vi		**11**			**21**	94
vii		**9**			**22**	31
viii		**9**			**10**	47[d]
ix		**13**			**23**	34[d,e]

[a] Suzuki reaction conditions: oxazole chloride (1 equiv), boronic acid (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), Na_2CO_3 (2 M aq, 4 equiv), DME (0.1 M) 80 °C, 48–64 h.

[b] Stille reaction conditions: oxazole chloride (1 equiv), organostannane (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), DMF (0.1 M), 100 °C, 48 h.

[c] Yield in parentheses based on recovered starting material.

[d] 1,4-Dioxane replaced DMF as the solvent, 100 °C, 3–6 h.

[e] The isomer of **13** with the alkene in conjugation with the oxazole was isolated in 42% yield.

position proceed relatively slowly with the need for portion-wise addition of the catalyst and organometallic reagent to push the reaction to completion.

Using these conditions, we have synthesised a range of 2,4-disubstituted oxazoles using both Stille and Suzuki coupling reactions (Table 2). The Suzuki conditions resulted in good to excellent yields of the coupled products (entries i–iv). Unfortunately, coupling with 3-thiophene boronic acid (entries iii and iv) proceeded particularly slowly leading to only a moderate yield of **19**, previously reported as being of biological interest.[10] However, in all cases the only materials, other than the desired product, isolated from the reaction mixture were the homocoupled compounds and starting material, and hence longer reaction times should give higher yields. Stille coupling proceeds well with $PdCl_2(PPh_3)_2$ as the catalyst, but at a much slower rate relative to the corresponding Suzuki coupling. With DMF as the solvent, reactions proceeded at an acceptable rate (entries v–vii), although with systems containing double bonds prone to migration into conjugation with the oxazole, such as **9**, DMF results in the formation of the migrated product **22** (entry vii). Acceptable yields of the nonmigrated product **10** can be obtained using 1,4-dioxane as the solvent system, still with some loss of yield due to the migration of the double bond (entry viii). In appropriate systems both Suzuki and Stille reactions can provide excellent yields of 2,4-disubstituted oxazoles (entries i and v).

We have described the synthesis of 4-bromomethyl-2-chlorooxazole **5** and shown its synthetic utility in the formation of a variety of 2,4-disubstituted oxazoles. For the initial reaction, Stille cross-coupling proves optimum, due to the pronounced selectivity for the 4-bromomethyl position. Both Suzuki and Stille reactions are effective for subsequent coupling at the 2-chloro position in excellent yields. We are currently investigating other palladium-catalysed coupling reactions, including one-pot variants, and applying this methodology to natural product synthesis.

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