Novel synthesis of oxindoles from carbamoyl chlorides *via* palladium catalysed cyclisation–anion capture

Mark R. Fielding,[a] Ronald Grigg*[a] and Christopher J. Urch[b]

[a] *Department of Chemistry, University of Leeds, Woodhouse Lane, Leeds, UK LS2 9JT. E-mail: R.Grigg@chem.leeds.ac.uk*

[b] *Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell, UK RG42 6ET*

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The synthesis of 3,3-disubstituted and 3-methyleneoxindoles by palladium(0) catalysed cyclisation of carbamoyl chlorides onto proximate alkene or alkyne groups has been achieved in good yields.

3,3-Disubstituted oxindoles are common structural motifs in a wide range of natural products. Gelsemine,[1] paraherquamides[2] and spirotryprostatins[3] represent classes that possess oxindole cores and have interesting biological profiles. 3-Methyleneoxindoles, on the other hand, are versatile intermediates in synthesis. Recently, Williams *et al.*[4] used a diasterospecific cycloaddition onto a methyleneoxindole in their total synthesis of spirotryprostatin B. Classically, spirooxindoles can be synthesised *via* an oxidative rearrangement of indoles[5] and methyleneoxindoles can be accessed by Wittig–Horner[6] type reactions of isatin. Oxindoles can conceptually be constructed by palladium catalysed processes in a number of ways. There are examples of intramolecular Heck and intramolecular cyclisation–anion capture reactions on acrylamide derivatives of 2-iodoanilines.[7] We have applied our palladium catalysed cyclisation–anion capture methodology to 3,3-disubstituted oxindoles (including spirooxindoles)[8] *via* formation of bond **a** (Fig. 1). We have also developed a 3-component process[9] which constructs bonds **a**, **b**, and **c**. We now describe palladium catalysed cyclisation–anion capture processes involving formation of bond **b** (Fig. 1).

The use of carbamoyl chlorides in palladium catalysed cross-coupling reactions with stannanes was reported by Jousseaume and Dubac.[10] Its use in Heck-type cyclisations[11] is rare, perhaps because the initial reports employed forcing conditions and toxic cosolvents for the synthesis of lactams. Our plan was to use 2-ethynyl- or 2-isopropenyl-phenylcarbamoyl chlorides as oxindole precursors (Fig. 1) in cyclisations which do not terminate *via* β-hydride elimination (as in Heck processes) but involve a group or atom transfer. This process (known as cyclisation–anion capture)[12] allows a large variety of groups to be introduced onto the oxindole. By this route, (*Z*)-3-methyleneoxindoles are stereospecifically formed and 3,3-disubstituted oxindoles can be potentially synthesised by a catalytic, enantioselective process.

The synthesis of the required carbamoyl chlorides was achieved from the appropriate 2-haloaniline in high overall yield (Scheme 1). 2-Iodoaniline **1** is converted to its *N*-benzyl derivative **2** using a reductive amination protocol. Treatment of

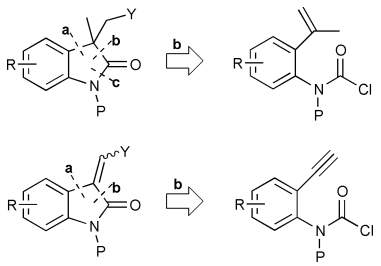
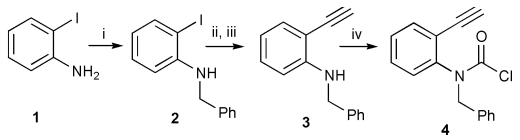


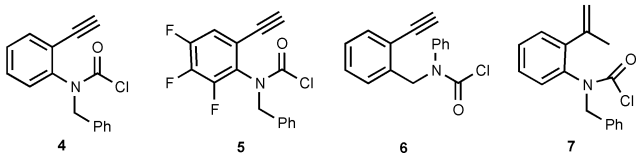
Fig. 1



Scheme 1 *Reagents and conditions*: i, PhCHO, MeOH, reflux then $NaBH_4$, reflux (45%, 86% based on 52% conv.); ii, TMSA, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, rt (90%); iii, TBAF, THF–H_2O, rt (91%); iv, $COCl_2$, $NaHCO_3$, DCM–H_2O, 0 °C (93%).

2 with a two step Sonagashira[13]-deprotection procedure then affords the 2-ethynyl derivative **3**. Finally, addition of phosgene[14] to aniline **3** at 0 °C for 10 min affords carbamoyl chloride **4**.

A range of carbamoyl chlorides **4**–**7** were synthesised in a similar way to provide a selection of 5- and 6-membered heterocycle precursors. These carbamoyl chlorides are air and moisture insensitive and can be purified on flash silica. Substrates **4** and **5** are 3-methyleneoxindole precursors, whilst **6**



is an example of a 6-ring isoquinolinone precursor. Carbamoyl chloride **7** was synthesised from commercially available 2-isopropenylaniline.

Initially, we focused on the use of tributylstannanes as anion capture agents for these substrates.[15] It was found that treatment of **4** with tributyl(2-thienyl)tin and $Pd(OAc)_2$–tris(2-furyl)phosphine in toluene at 50 °C for 5 min affords the desired 3-methyleneoxindole **8** in 88% yield (Scheme 2). Repetition of this latter reaction using 1 mol% $Pd(OAc)_2$–2 mol% tris(2-furyl)phosphine and a reaction time of 30 min afforded **8** in 91% yield emphasising the scope for considerable reduction in catalyst loading. The use of tributyl(phenylethynyl)tin also resulted in a high yield of product (81%), whilst vinyl transfer affords a 4 : 3 mixture of geometrical isomers **10** and **11** in 76% overall yield. Cyclisation–anion capture employing tributyl(2-furyl)tin was also complete within 5 min at 50 °C, and afforded (*Z*) **12** in 78% yield.

This methodology can also be extended to 6-ring cyclisation–anion capture and to the synthesis of 3,3-disubstituted oxindoles (Scheme 3).

Cyclisation of **6** affords **13** (87%), a 4-methyleneisoquinolin-3-one in 5 min at 50 °C. However, cyclisation onto the isopropenyl group of **7** to form **14** is much slower (4 h), but proceeds in excellent yield (84%). The use of boronic acids as anion capture reagents[8] is currently being studied. A preliminary study involving **7** and phenylboronic acid afforded **15** (50%) (Scheme 3). This reaction was considerably slower (50 h, 90 °C) than those involving organostannane anion capture reagents and since a small amount of water was present

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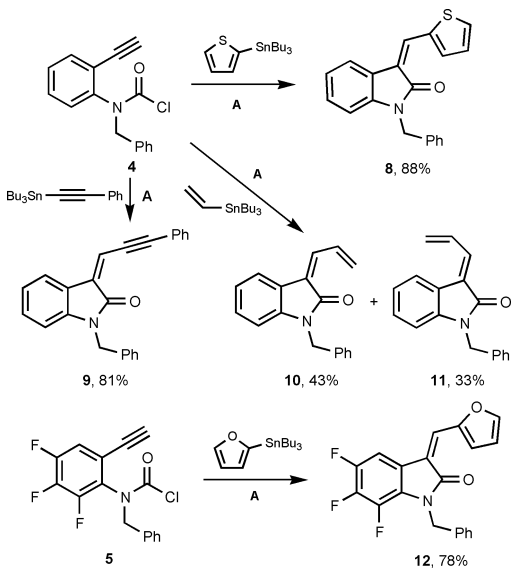
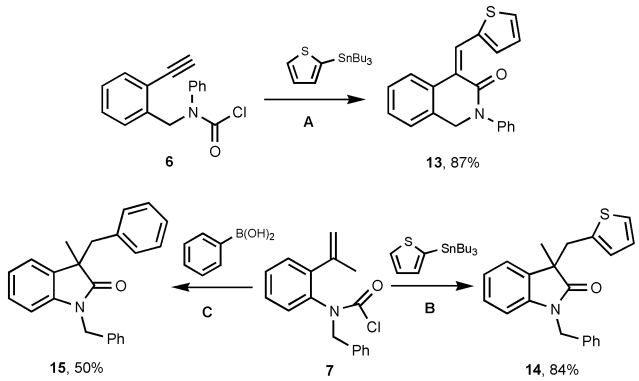


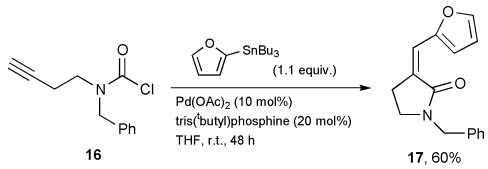
Scheme 2 *Reagents and conditions*: **A** = $Pd(OAc)_2$ (10 mol%), tris(2-furyl)phosphine (20 mol%), 1.1 equiv. Bu_3SnY, toluene, 50 °C. All reactions were complete within 5 min at 50 °C.



Scheme 3 *Reagents and conditions*: **A** = $Pd(OAc)_2$ (10 mol%), tris(2-furyl)phosphine (20 mol%), 1.1 equiv. Bu_3SnY, toluene, 50 °C, 5 min; **B** = $Pd(OAc)_2$ (10 mol%), tris(2-furyl)phosphine (20 mol%), 1.1 equiv. Bu_3SnY, toluene, 85 °C, 4 h; **C** = $Pd(OAc)_2$ (10 mol%), triphenylphosphine (20 mol%), 2 equiv. $PhB(OH)_2$, toluene, water (2 drops), 90 °C, 50 h.

(Scheme 3, **C**) there was some destruction of the carbamoyl chloride **7**.

The presence of the benzene ring in the above examples is one factor promoting the rapid cyclisation of these carbamoyl chlorides. To extend the scope of this cyclisation–anion capture methodology, we synthesised an example of a non-aryl based carbamoyl chloride. Substrate **16** was derived from but-3-yn-1-ol *via* its tosylate and reacted with benzylamine and then phosgene[14] in the normal fashion. At the typical reaction temperature of 50 °C, only 35% of product **17** was isolated. However, replacing tris(2-furyl)phosphine by the electron rich



tris(*tert*-butyl)phosphine gave, over 48 h at rt, a 60% yield of lactam **17**.

The two strategic bond formation modes (Fig. 1, **a** and **b**) allow both (*E*)- and (*Z*)-3-methyleneoxindoles to be accessed stereoselectively. Thus formation of bond **a** by palladium catalysed cyclisation onto a proximate alkyne with anion capture affords *E*-isomers[16] whilst formation of bond **b** by palladium catalysed cyclisation affords *Z*-isomers.

In summary, these preliminary results on the palladium catalysed cyclisation–anion capture of carbamoyl chlorides demonstrate that (*Z*)-3-methylene- and 3,3-disubstituted oxindoles can be accessed under mild conditions in high yields. Further studies of these and related processes are in hand.

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