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A multi-component coupling approach to benzo[*b*]furans and indoles†

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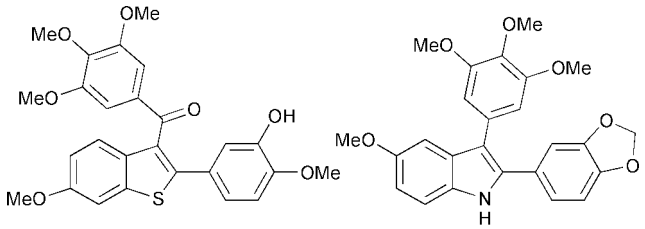
A single step access to multiply substituted benzo[*b*]furans and indoles has been developed.

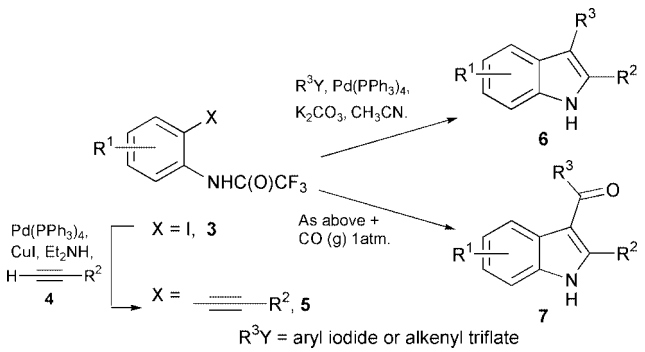
Indoles, benzo[*b*]furans and benzo[*b*]thiophenes are structural cores to a host of bioactive compounds in pharmaceutical use or development. Recently, we described a novel, concise approach to benzo[*b*]thiophenes.[1] This synthesis was used to prepare the tubulin polymerisation inhibitor (TPI) **1**.[1,2] TPIs are valued for



1 **2**

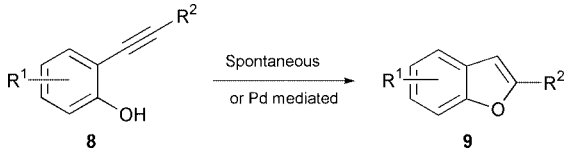
their capacity to inhibit the proliferation of cancer cells and to target tumour vascular endothelial cells.[2c] Medarde *et al.* recently described some cytotoxic 2,3-diarylindole systems, *e.g.* **2**, that were also believed to be TPIs.[3] In our ongoing examination of the structure–activity relationship (SAR) of TPIs such as **1** and **2**,[1,4] we required a concise, flexible access to 2,3-diaryl (and aroyl) benzo[*b*]furans and indoles to complement our access to benzo[*b*]thiophenes. Here we describe a palladium mediated, one-pot, multi-component coupling process that gives direct access to 2,3-disubstituted benzo[*b*]furans and indoles.

Cacchi and co-workers previously reported a two step synthesis of 2,3-disubstituted indoles from *o*-iodotrifluoroacetanilides **3** (Scheme 1).[5] This involves initial Sonogashira coupling of **3** to a terminal alkyne **4** to give an *o*-alkynyltrifluoroacetanilide **5**, which undergoes heteroannulative coupling to aryl iodides and alkenyl triflates to give indoles **6** (R^3 = aryl or alkenyl respectively). The trifluoroacyl group is lost during the coupling process. When performed under an atmosphere of CO gas, heteroannulation proceeds in a carbonylative fashion to provide the corresponding 3-acylindoles **7**.



Scheme 1

This access to indoles **6** and **7** was generally quite efficient. However, extending this approach to the synthesis of 2,3-disubstituted benzo[*b*]furans from *o*-iodophenols proved problematic.[6] The propensity of intermediate *o*-alkynylphenols **8** to undergo cyclisation to simple 2-substituted benzo[*b*]furans **9**, particularly in the presence of palladium, required that the phenolic hydroxy be protected during the initial coupling of the alkyne to the *o*-iodophenol [eqn. (1)].[6] Cyclisation of **8** to **9** was

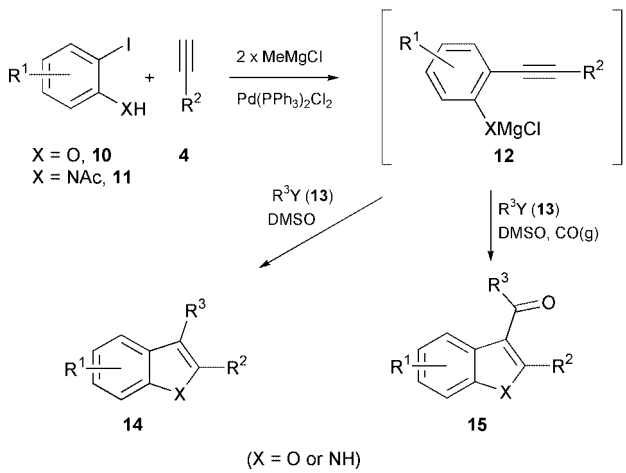


(1)

also a problem during deprotection and attempted heteroannulative coupling. As a result the overall yield of 2,3-disubstituted benzo[*b*]furan obtained from this multi-step sequence was generally very low. The process was also quite specific to the use of alkenyl triflates as substrates in the heteroannulative coupling reaction and for electron withdrawing groups in the *o*-alkynylphenol.[6]

We sought to improve this access to benzo[*b*]furans by removing any possibility of cyclisation of the *o*-alkynylphenols **8** to 2-substituted benzo[*b*]furans **9** and by reducing the number of steps required. This led to our development of a one-pot, multi-component coupling procedure (Scheme 2). This involves initial deprotonation of a mixture of *o*-iodophenol **10** and terminal alkyne **4** with MeMgCl to give the corresponding magnesium phenolate and magnesium acetylide respectively (not shown). Addition of $Pd(PPh_3)_2Cl_2$ (3 mol%) and heating leads to a coupling to give *o*-alkynylphenoxy magnesium chloride **12** (X = O). Dilution with an equal volume of DMSO and addition of a suitable coupling partner R^3Y (**13**) then gives the heteroannulatively coupled product **14** (X = O) or **15** (X = O) (under carbonylative conditions).

Alkenyl bromides, alkenyl iodides, and aryl iodides all proved to be effective coupling partners in heteroannulation (Table 1, entries 1–5).† The low yield of the product involving



Scheme 2

† Electronic supplementary information (ESI) available: experimental procedures and spectroscopic data for **14a–h**, **15a** and **16**. See http://www.rsc.org/suppdata/cc/b1/b104624c/

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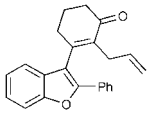
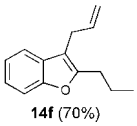
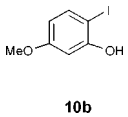
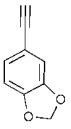
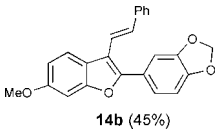
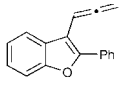
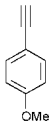
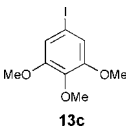
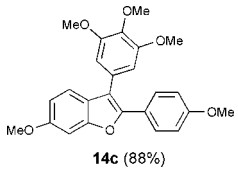
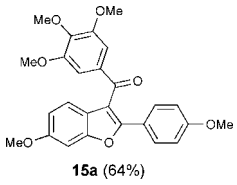
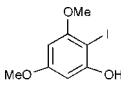
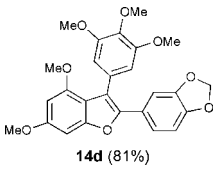
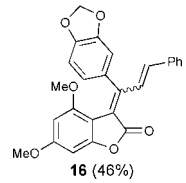
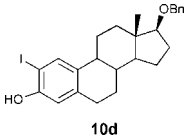
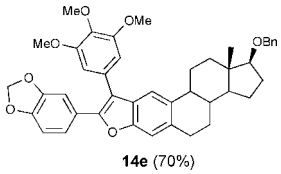
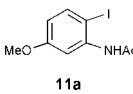
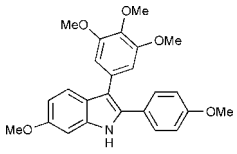
Table 1 Multi-component coupling reaction for the formation of benzo[*b*]furans and indoles (see also Scheme 1)[a]

	Components					Components			
Entry	**10**	**4**	**13**	Product (yield (%))	Entry	**10/11**	**4**	**13**	Product (yield (%))
1	 **10a**	 **4a**	 **13a**	 **14a** (78%)	6	**10a**	 **4d**	 **13d**	 **14f** (70%)
2	 **10b**	 **4b**	 **13b**	 **14b** (45%)	7[b]	**10a**	**4a**	 **13e**	 **14g** (64%)
3	**10b**	 **4c**	 **13c**	 **14c** (88%)	8[c]	**10b**	**4c**	**13c** + CO(g)	 **15a** (64%)
4	 **10c**	**4b**	**13c**	 **14d** (81%)	9[c]	**10c**	**4b**	**13b** + CO(g)	 **16** (46%)
5	 **10d**	**4b**	**13c**	 **14e** (70%)	10	 **11a**	**4c**	**13c**	 **14h** (85%)

[a] All reactions were performed as follows (unless otherwise stated): (i) **10** (or **11**), **4**, 2 × MeMgCl in THF, 0 °C; (ii) $Pd(PPh_3)_2Cl_2$ 3 mol%, 65 °C, 1–2 h; (iii) cool to 18 °C, add **13**, dilute with an equal volume of DMSO and heat to 80–95 °C, 4–19 h. [b] CH_3CN was used as a solvent in place of DMSO and a further 1.3 equiv. of **12e** was added after 2 h. [c] CO (g) 1 atm was introduced upon addition of **13** and DMSO and the reaction heated to 80–95 °C for 20 h.

the styrenyl iodide **13b** is expected to have resulted from the instability of this iodide under the reaction conditions, that is, in the presence of palladium at elevated temperatures. Good yields were also obtained when allyl acetate **13d** and propargyl tosylate **13e** (gives an allenic product) were used as coupling partners (entries 6 and 7).

When the coupling reaction that gave rise to **14c** was repeated, using a carbon monoxide atmosphere at the point of introduction of **13c**, the heteroannulative coupling proceeded in a carbonylative fashion to give **15a** in good yield (entry 8). There were no signs of formation of significant quantities of ester (esterification of the *o*-alkynylphenol) or the simple 2-substituted benzo[*b*]furan **9**, which dominated under the reaction conditions employed by Cacchi and co-workers.[6] Heteroannulative coupling involving the styrenyl iodide **13b** under such carbonylative conditions gave rise to the 3-alkylidenebenzo[*b*]furan-2-one **16** as the major product (entry 9). Benzo[*b*]furanone **16** has clearly resulted from an alternative coupling pathway. Arcadi *et al*. recently described a similar reaction involving vinyl triflates with *o*-ethynylphenols and proposed a mechanism of formation of the benzo[*b*]furanones.[7]

Although the two step process developed by Cacchi for the synthesis of indoles was quite efficient we were gratified to find that our approach to benzo[*b*]furans could also be extended to a one-pot access to indoles as is exemplified by our efficient preparation of **14h** (entry 10).

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Notes and references

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