Pergamon

Tetrahedron Letters 42 (2001) 9081–9084

TETRAHEDRON LETTERS

A Suzuki coupling approach to bufadienolides

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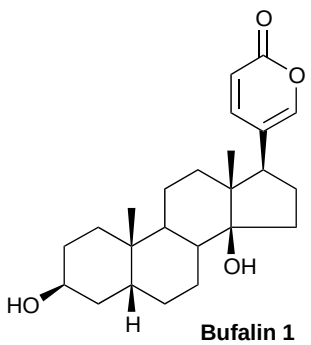
Received 12 September 2001; revised 9 October 2001; accepted 19 October 2001

Abstract—A high yielding route to bufadienolide type steroids using a novel Suzuki coupling reaction between a range of steroid vinyl triflates and 2-pyrone-5-boronate **11** is presented.

Synthetic routes to the bufadienolide group of steroids are important due to the powerful biological activity of these compounds[1] and their proposed role in controlling the mammalian sodium pump.[2] Bufadienolides are characterised by a 2-pyrone unit connected at the 5-position to the C-17 position of a steroid nucleus and exemplified by the toad venom bufalin **1** (Fig. 1).

Initial synthetic routes to bufadienolides were based on linear strategies, building up a suitable five carbon chain at the C-17 position of a steroid prior to cyclisation and subsequent modification of the pyrone ring.[3] Meinwald and Liu[4] recently disclosed a convergent synthesis whereby 5-(trimethylstannyl)-2-pyrone **3** was coupled to a suitably modified estrone nucleus **2** using the Pd(0)-catalysed cross coupling methodology studied by Stille.[5] The coupled product **4** was then deprotected prior to catalytic hydrogenation of the C16–C17 double bond to give the bufadienolide **6** (Scheme 1).



Bufalin 1

Figure 1.

Current work in our group requires various bufadienolides derived from androsterone and its stereoisomers. We have followed the methodology of Meinwald and Liu,[4] extending it to androsterone derived vinyl triflates, and shown it to work in these cases. However, the use of highly toxic tin reagents was a serious concern to us, especially when the possibility of in vivo testing was taken into account. Even though the desired steroids are subjected to several purification steps after the Stille coupling, organotin residues are particularly difficult to remove completely. The use of aryl boronic acids in similar Pd(0)-catalysed cross couplings has been extensively studied by Suzuki[6] and many others, and there have been recent reports of the coupling of 5-bromo-2-pyrone **9** to various aryl boronic acids.[7] We felt that a 5-boron substituted 2-pyrone reagent would give more synthetic flexibility and so we decided to investigate the preparation of a suitable 2-pyrone boronic acid or boronate ester and to study the coupling reaction of this compound to steroid vinyl triflates.

5-Bromo-2-pyrone **9** is a convenient source of the 2-pyrone sub-unit and its synthesis has been reported by two different routes.[8] In our experience free radical dibromination of 2-pyrone **7** followed by base elimination of HBr proved the best way to obtain 5-bromo-2-pyrone **9** in good yield and purity (Scheme 2). A recent report by Masuda and co-workers[9] reported the coupling of pinacolborane **10** to various aryl halides in the presence of catalytic $PdCl_2$(dppf) and NEt_3 in dioxane at 80°C to give the corresponding aryl boronates in high yields. When we repeated these reaction conditions with 5-bromo-2-pyrone there was little apparent evidence of reaction, although GCMS analysis indicated a very small amount of the required product had been formed. Modifying the conditions by changing the catalyst to $PdCl_2(PPh_3)_2$ and carrying out the reaction in

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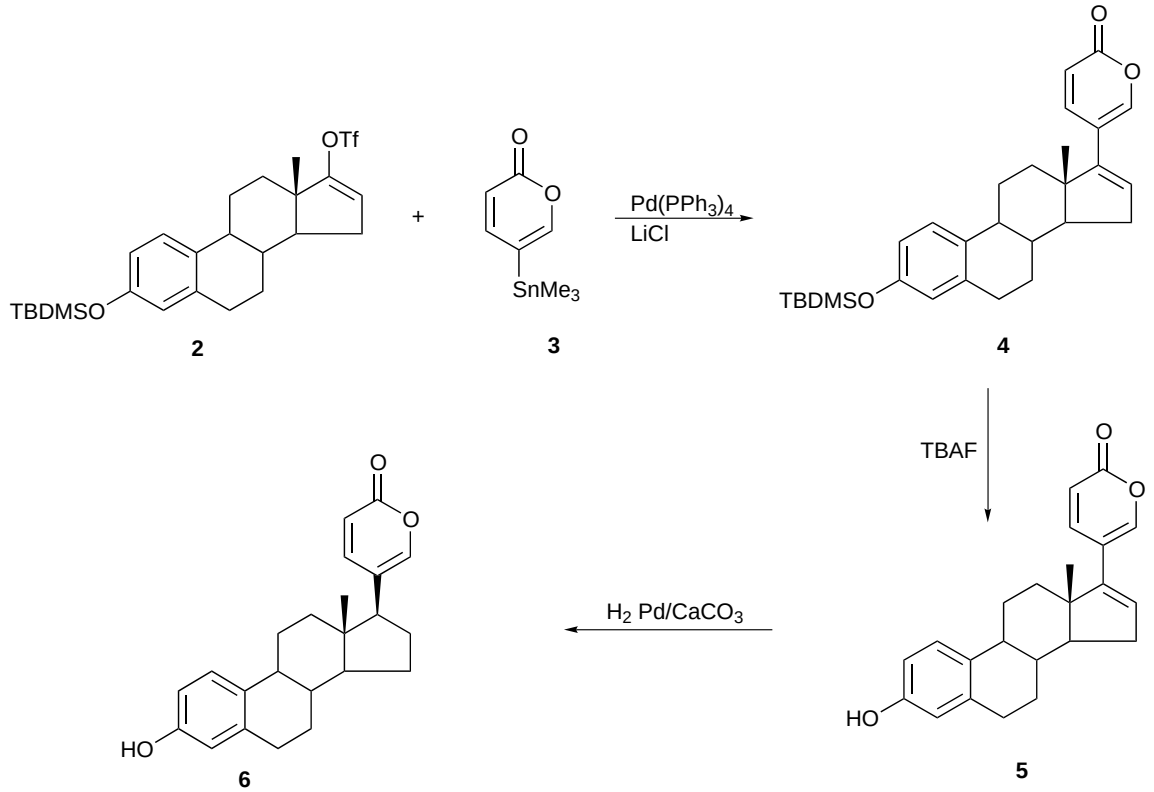
PII: S0040-4039(01)01980-3

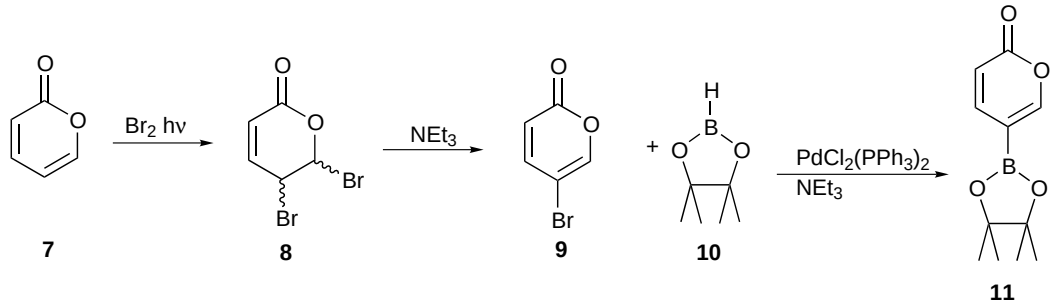


Scheme 1.

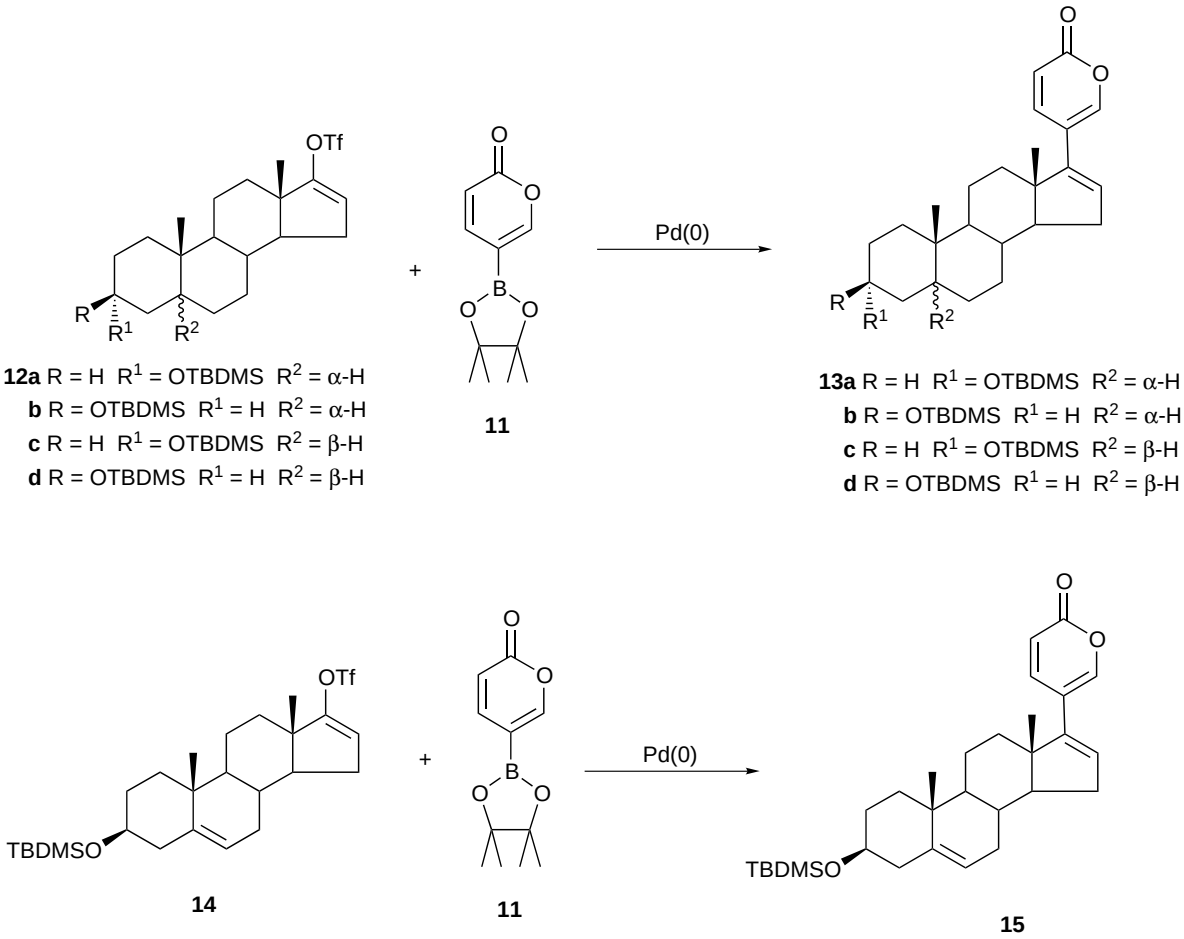
toluene at reflux temperature led to a good yield (70%) of the desired 2-pyrone-5-boronate **11** (Scheme 2).

The palladium-catalysed cross coupling reaction of **11** with a range of steroidal vinyl triflates could now be investigated (Scheme 3). Four commercially available androsterones, one dehydroandrosterone and estrone were modified in the same way as described by Meinwald and Liu,[4] i.e. TBDMS protection of the secondary alcohol at C-3 followed by formation of the vinyl triflate, both reactions proceeding in >90% yield for all our examples.

We investigated various combinations of solvent, catalyst and base for the coupling reaction and these are summarised in Table 1. Initially standard Suzuki[10] coupling conditions were tried (entry 1) but no coupling was observed. Coupling reactions between aryl boronates and triflates have been reported in the literature[11] using the $PdCl_2$(dppf) catalyst and this proved to be successful in our examples. Use of an organic base (entries 2 and 3) gave low yields of coupled product but switching to an inorganic base showed an immediate improvement with K_3PO_4 being superior to KF (entries 4–6). It proved essential to finely crush the K_3PO_4 to achieve successful coupling. Optimum conditions for the coupling gave yields in the range 75–91% for the five androsterone derivatives **12a–d**, **14** (entries 7–11).[12] These conditions were less effective for coupling to the estrone derived vinyl triflate **2** and there was a tendency for the coupled product to be deprotected in situ (entry 12). As our interest lay in the androsterone-derived products, coupling of **11** to **2** was not optimised. Hydrogenation of the C16–C17 double bond in **13a–d**, **15** to give bufadienolides was achieved straightforwardly using the conditions reported by Meinwald and Liu.[4]



Scheme 2.



Scheme 3.

Table 1. Coupling reaction of **11** with steroidal vinyl triflates, Scheme 3

Entry	Steroid	**11** (equiv.)	Solvent	Catalyst (equiv.)	Base (equiv.)	Time (h)	*T* (°C)	Product (yield)
1	**12d**	1.1	Dioxane	$Pd(PPh_3)_4$ (0.03)	K_3PO_4 (1.5)	6	90	None
2	**12b**	1.0	DMF	$PdCl_2$(dppf) (0.03)	NEt_3 (2.0)	6	60	**13b** (27%)
3	**2**	1.0	DMF	$PdCl_2$(dppf) (0.03)	NEt_3 (2.0)	6	60	**4** (5%)
4	**12b**	1.0	DMF	$PdCl_2$(dppf) (0.03)	KF (1.0)	18	60	**13b** (41%)
5	**14**	1.5	DMF	$PdCl_2$(dppf) (0.03)	KF (1.0)	18	60	**15** (42%)
6	**2**	1.0	DMF	$PdCl_2$(dppf) (0.03)	K_3PO_4 (1.5)	6	60	**4** (52%)
7	**12a**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**13a** (75%)
8	**12b**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**13b** (76%)
9	**12c**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**13c** (85%)
10	**12d**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**13d** (91%)
11	**14**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**15** (84%)
12	**2**	1.3	DMF	$PdCl_2$(dppf) (0.1)	K_3PO_4 (3.5)	6	60	**5** (35%)

In summary, we have shown that the Pd(0)-mediated coupling of 2-pyrone-5-boronate **11** to a range of steroid vinyl triflates is an efficient method of preparing bufadienolide type steroids without the use of toxic tin reagents and hence avoids the risk of contamination of products with tin residues.

Acknowledgements

We should like to acknowledge financial support from the Special Trustees for St Thomas' Hospital.

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12. Typical procedure for the Suzuki couplings: The vinyl triflate of TBDMS protected 3β-etiocholanolone **12d** (0.24 g, 0.45 mmol), 2-pyrone-5-boronate **11** (0.14 g, 0.6 mmol), and $PdCl_2$(dppf) (40 mg, 0.045 mmol) were dissolved in dry DMF (5 ml) under a N_2 atmosphere. Some gentle warming was needed to aid dissolution. Finely crushed K_3PO_4 (0.3 g, 1.4 mmol) was added to the DMF solution and this slurry was heated to 60°C for 6 h. The DMF was removed under reduced pressure to give a dark solid which was initially purified by dissolving in DCM and filtering through a plug of silica, followed by a further elution of DCM (100 ml). The solvent was removed under reduced pressure to give a brown crystalline solid that was further purified by flash column chromatography with DCM as eluent to yield the coupled product **13d** (0.2 g, 0.41 mmol, 91%), mp 172–174°C. δ_H ($CDCl_3$, 300 MHz) 0.00 (6H, s), 0.87 (9H, s), 0.89 (3H, s), 0.96 (3H, s), 1.05–1.95 (19H), 2.18 (1H, m), 4.02 (1H, br. s), 5.85 (1H, m), 6.30 (1H, dd, *J* 9.6, 0.9), 7.42 (1H, dd, *J* 9.6, 2.4) and 7.48 (1H, br. s); δ_C ($CDCl_3$, 75 MHz) −4.8, 16.4, 18.1, 21.1, 23.9, 25.9, 26.4, 26.8, 28.6, 29.9, 31.5, 34.2, 34.5, 35.2, 35.8, 36.6, 40.3, 47.4, 57.5, 67.3, 116.2, 116.4, 128.7, 144.3, 146.6, 147.1 and 161.5; *m*/*z* (electrospray) 483 (MH^+).