Pergamon

Tetrahedron Letters 43 (2002) 8853–8857

TETRAHEDRON LETTERS

An efficient synthesis of 4-alkenyl/alkynyl-6-methyl-2-pyrones via Pd-catalysed coupling on 4-bromo-6-methyl-2-pyrone

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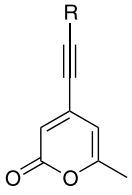
Received 28 August 2002; revised 23 September 2002; accepted 4 October 2002

Abstract—We herein report the efficient syntheses of biologically active 4-alkenyl- and 4-alkynyl-6-methyl-2-pyrones using Pd-catalysed coupling procedures. A palladium on carbon/triphenylphosphine combination is shown to be the most effective catalyst for Sonogashira cross-coupling of several terminal acetylenes with 4-bromo-6-methyl-2-pyrone in yields of up to 95%.

The 2-pyrone moiety is found in a large number of naturally-occurring biologically active compounds.[1] It finds a wide variety of applications in organic synthesis as a cyclobutane precursor,[2] a diene component in Diels–Alder reactions,[3] and as a precursor to other heterocyclic systems.[4] Despite their synthetic utility, the synthesis and construction of substituted 2-pyrones is fraught with difficulties, often requiring a multi-step synthesis via an acyclic precursor. Methods for the introduction of substituents within the preformed pyrone ring via electrophilic or nucleophilic substitution are cumbersome. These reactions generally lead to ring-opening and rearrangements and the pyrone ring is impossible to regenerate. Indeed, few direct substitutions onto the 2-pyrone ring have been reported.[5] There has been notable recent interest in the synthesis of 3-alkynyl-5-bromo-2-pyrones.[6] Our interest in this area stems from the associated antimicrobial, human ovarium carcinoma (A2780) and human chronic myelogenous leukaemia (K562) inhibitory properties of 4-alkenyl/alkynyl-substituted-6-methyl-2-pyrones (Fig. 1).[7]

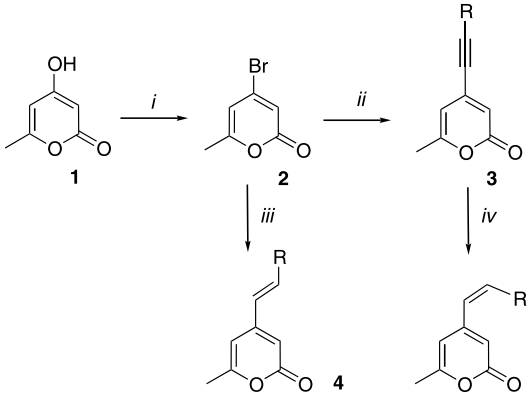
The promising anti-cancer and anti-leukaemia activities prompted us to devise efficient synthetic routes to these compounds using a variety of Pd-catalysed coupling procedures (Scheme 1).

To the best of our knowledge there is only one report on the oxidative addition of Pd(0)-based catalysts to the C4-position of appropriately halogenated pyrones.[8] Indeed, there is every reason to suspect that the C4-carbon centre is very reactive towards oxidative addition



	A2780	K562 (IC_{50})
R = H,	3.1 μM	2.0 μM
R = Ph,	1.8 μM	4.0 μM
R = CH_2OTHP,	2.1 μM	4.0 μM

Figure 1. Biologically active 2-pyrones.



Scheme 1. Synthesis of 4-alkenyl and 4-alkynyl pyrones. *Reagents and conditions*: (i) PBr_3, DMF, 70°C; (ii) [Pd] cat., CuI, Et_3N, RC≡CH; (iii) [Pd] cat., RCH=CHM (*E*), Solv.; (iv) Pd/C, H_2, quinoline, benzene.

Keywords: pyrones; palladium; organometallic couplings.

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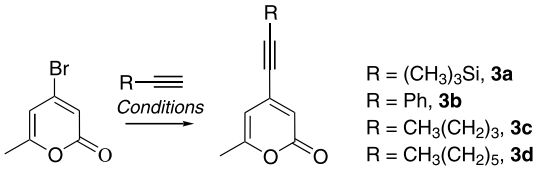
PII: S0040-4039(02)02207-4

and we thus initially screened a variety of conditions for Sonogashira alkynylations of 4-bromo-6-methyl-2-pyrone (available in 79% yield using PBr_3 in DMF at 70°C) with various terminal alkynes to provide a series of 4-alkynyl-6-methyl-2-pyrones (**3a**–**d**) (Table 1).[9]

Initial investigations employing the standard catalyst for Sonogashira reactions; bis(triphenylphosphine)-palladium(II) chloride $(PPh_3)_2PdCl_2$ proved unsuccessful in a variety of solvents (entries 1–4, Table 1). The poor catalytic activity was surprising, as the analogous Sonogashira coupling of pyrones at the 3- and 5-positions are facile using this catalyst, particularly where DMF is employed as the reaction solvent.[6] Switching the solvent to DMF failed to improve our yields. We next focussed attention on the $Pd(OAc)_2/PPh_3$ pro-catalytic system to generate formally a $[Pd(0)(PPh_3)_2]$ species in situ (entries 5–8, Table 1) which gave the coupled products in satisfactory yields. Employment of the air and light sensitive $Pd(PPh_3)_4$ resulted in similar yields (entries 9–12, Table 1). Switching to the more stable Pd(0) complex, $Pd_2dba_3{\cdot}CHCl_3$, gave the coupled products in much better yields (entries 13–16, Table 1). But to our delight we found that use of a Pd/C and PPh_3 combination could be used with great success.

Table 1. Sonogashira couplings[a]



Entry	Catalyst system	R	Yield (%)
1	$Pd(PPh_3)_2Cl_2/CuI/Et_3N$[b]	$(CH_3)_3Si$	0
2	$Pd(PPh_3)_2Cl_2/CuI/Et_3N$[b]	Ph	Trace
3	$Pd(PPh_3)_2Cl_2/CuI/Et_3N/THF$[b]	Ph	12
4	$Pd(PPh_3)_2Cl_2/CuI/Et_3N/DMF$[b]	Ph	Trace
5	$Pd(OAc)_2/PPh_3/CuI/Et_3N$[b]	$(CH_3)_3Si$	50
6	$Pd(OAc)_2/PPh_3/CuI/Et_3N$[b]	Ph	43
7	$Pd(OAc)_2/PPh_3/CuI/Et_3N$[b]	$CH_3(CH_2)_3$	48
8	$Pd(OAc)_2/PPh_3/CuI/Et_3N$[b]	$CH_3(CH_2)_5$	27
9	$Pd(PPh_3)_4/CuI/Et_3N$[c]	$(CH_3)_3Si$	47
10	$Pd(PPh_3)_4/CuI/Et_3N$[c]	Ph	32
11	$Pd(PPh_3)_4/CuI/Et_3N$[c]	$CH_3(CH_2)_3$	52
12	$Pd(PPh_3)_4/CuI/Et_3N$[c]	$CH_3(CH_2)_5$	53
13	$Pd_2dba_3{\cdot}CHCl_3/PPh_3/CuI/Et_3N$[d]	$(CH_3)_3Si$	69
14	$Pd_2dba_3{\cdot}CHCl_3/PPh_3/CuI/Et_3N$[d]	Ph	73
15	$Pd_2dba_3{\cdot}CHCl_3/PPh_3/CuI/Et_3N$[d]	$CH_3(CH_2)_3$	62
16	$Pd_2dba_3{\cdot}CHCl_3/PPh_3/CuI/Et_3N$[d]	$CH_3(CH_2)_5$	56
17	$Pd–C/PPh_3/CuI/Et_3N$[e]	$(CH_3)_3Si$	82
18	$Pd–C/PPh_3/CuI/Et_3N$[e]	Ph	74
19	$Pd–C/PPh_3/CuI/Et_3N$[e]	$CH_3(CH_2)_3$	77
20	$Pd–C/PPh_3/CuI/Et_3N$[e]	$CH_3(CH_2)_5$	73

[a] All coupling reactions were conducted at reflux with dry Et_3N and dry CH_3CN (2.5:1.5), CuI (4 mol%) under N_2 for 3 h. CH_3CN was used unless stated.
[b] 6 mol% [Pd] catalyst, 18 mol% PPh_3.
[c] 6 mol% [Pd] catalyst.
[d] 2.5 mol% [Pd] catalyst, 15 mol% PPh_3.
[e] 10% Pd/C (20 wt%), PPh_3 (25 wt%).

Using the Pd/C and PPh_3 catalyst combination we explored the synthesis of a range of alkynyl coupled products (**3e**–**m**) (Table 2).

To the best of our knowledge this is the first time that the true scope of the Pd/C and PPh_3 catalyst system has been shown to have such a dramatic effect for any Pd-catalysed cross-coupling reaction. Note that only 2 mol% of Pd is used under these conditions.

From inspection of Table 2 (entries 1 and 2) it can be seen that simple aliphatic alkynes couple in good yields, compare also entries 19 and 20, Table 1. The low yields observed for propargyl alcohol and *p*-aminophenylacetylene (entries 3 and 5, Table 2) may be attributed to the presence of easily removable protons and subsequent inhibition of the catalyst. However, having said that, Cho and co-workers[6b] were able to couple the latter alkyne with 3,5-dibromo-2-pyrone using DMF as a solvent and thus H-bonding may have a deleterious effect on the catalyst activity in CH_3CN. For entry 5 (Table 2) there is also the possibility of competing pyridone and oligomer formation. Protection of both the alcohol as its tetrahydropyranyl ether and the amine as the acetamide (entries 4 and 6, Table 2, respectively) saw a dramatic increase in the yields. The unreactivity of propargyl acetate should be noted. Some intriguing examples are entries 7 and 8 (Table 2). Both the nitro and acetyl groups are electron-withdrawing but give significantly different yields. A comparison of other Pd(0) catalysts was made to see whether the effect was independent of the choice of catalyst (Table 3).

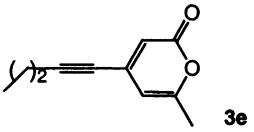
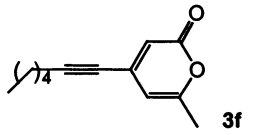
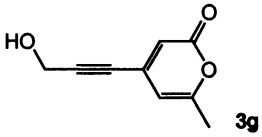
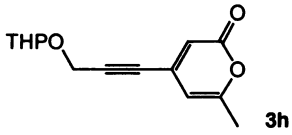
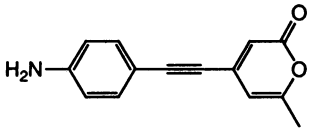
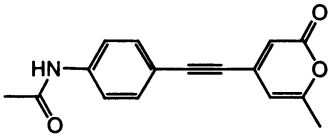
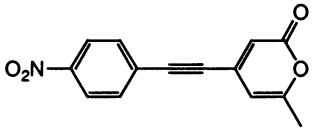
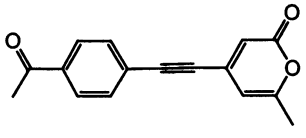
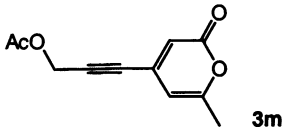
The most efficient catalyst was found to be $Pd(PPh_3)_4$ where >99% conversion of the coupled product for *p*-nitrophenylacetylene was observed by ^1H NMR. The large change in yields of one electron-withdrawing group with another is observed for each catalyst and therefore the yields are independent of choice of catalyst. It is believed that the acetate is coordinating to Pd and thereby deactivating the catalyst. This may also explain why propargyl acetate was likewise inactive.

Deprotection of 4-TMS-ethynyl-6-methyl-2-pyrone **3a** to generate 4-ethynyl-6-methyl-2-pyrone **6** was performed with a view to coupling our alkyne unit with a large variety of alkenyl and aryl halides (Scheme 2).

Standard silyl cleavage using methanolic KOH and 1 M solutions of tetrabutylammonium fluoride (TBAF) at room temperature resulted in spontaneous decomposition of the 2-pyrone unit. For TBAF the reaction could be conducted at −78°C for 2 h to give the deprotected alkyne **6** in 80% yield. Unfortunately we have so far been unable to couple this pyrone with aryl halides under a variety of standard conditions (Et_3N as base

and either CH_3CN, THF or DMF at reflux) using $Pd(OAc)_2/PPh_3$ or $Pd(PPh_3)_4$ catalysts. We believe this is due to the high reactivity of pyrone **6** with basic solvents, in which immediate decomposition is observed, even in solvents, such as diethyl ether and ethanol at temperatures of −30°C. The pyrone is stable in weakly acidic solvents such as chloroform and hexane, respectively. For this reason it is important to note that the isolation of this product must be done using non-polar, neutral solvents.

Table 2. Further Sonogashira couplings using the Pd/C/PPh_3 combination[a]

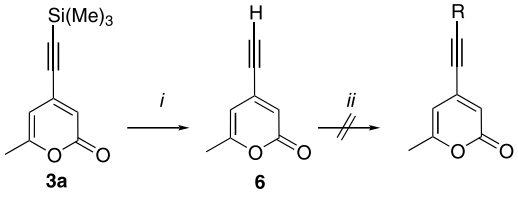
Entry	Coupled product	Yield
1	 **3e**	72
2	 **3f**	79
3	 **3g**	4.9
4	 **3h**	81
5	 **3i**	21
6	 **3j**	95
7	 **3k**	95
8	 **3l**	35
9	 **3m**	0

[a] Using conditions *e* (Table 1).

Table 3. Effect of [Pd] catalyst on yields of **3k** and **3l**[a]

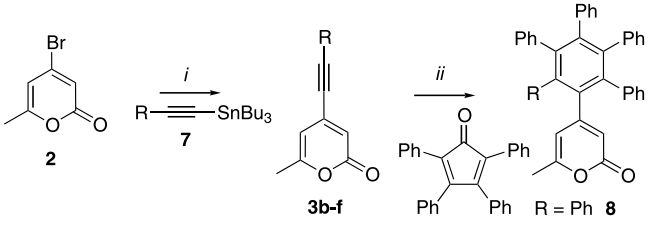
Entry	Catalyst system	Alkyne (R)	Yield[b] (%)
1	$Pd(OAc)_2/PPh_3/CuI/Et_3N$	*p*-NO_2-Ph	90 (98)
2	$Pd(PPh_3)_4/CuI/Et_3N$	*p*-NO_2-Ph	95 (>99)
3	Pd–C/PPh_3/CuI/Et_3N	*p*-NO_2-Ph	86 (94)
4	$Pd(OAc)_2/PPh_3/CuI/Et_3N$	*p*-CH_3CO-Ph	26
5	$Pd(PPh_3)_4/CuI/Et_3N$	*p*-CH_3CO-Ph	35
6	Pd–C/PPh_3/CuI/Et_3N	*p*-CH_3CO-Ph	35

[a] Conditions as for Table 1 and the respective catalyst systems.
[b] Yields are based on pure isolated products. Yields in parenthesis are by NMR.

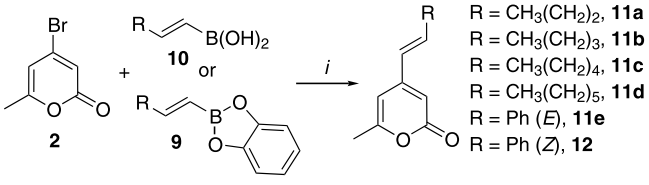


Scheme 2. *Reagents and conditions*: (i) TBAF (1 M), THF, −78°C; (ii) [Pd] cat., CuI, Et_3N, CH_3CN.

It was found that we could couple **2** to alkynylstannanes **7** using a modified Stille procedure[10] employing $(PPh_3)_2PdCl_2$ in THF/diisopropylamine (DIPA) (1:3 ratio) to give 4-phenylethynyl-6-methyl-2-pyrone **3b** in 75% yield (Scheme 3). We were able to extend this to other alkynes, where $R = CH_3(CH_2)_n$, $n = 2$, 3, 4 and 5, **3c–f**) and good yields were observed (56–63%). Of particular interest is the utility of these alkynylpyrones as a dienophile in Diels–Alder reactions with electron-deficient dienes.



Scheme 3. *Reagents and conditions*: (i) $(PPh_3)_2PdCl_2$ (5 mol%), THF/DIPA; (ii) 300°C, benzophenone.



Scheme 4. Suzuki cross-coupling of 4-bromo-6-methyl-2-pyrone **2**. *Reagents and conditions*: (i) $Pd(OAc)_2$ (6 mol%), PPh_3 (18 mol%), **9** or **10**, benzene, Δ, 6 h.

Table 4. Suzuki cross-coupling of alkenyl benzodioxaboroles and boronic acids[a]

Entry	Alkene (R)	% Yield from benzodioxaboroles	% Yield from boronic acids
1	$CH_3(CH_2)_2$ (**11a**)	35	58
2	$CH_3(CH_2)_3$ (**11b**)	32	66
3	$CH_3(CH_2)_4$ (**11c**)	41	60
4	$CH_3(CH_2)_5$ (**11d**)	32	56
5	Ph (*E*) (**11e**)	31	27

[a] Conditions: $Pd(OAc)_2$ (6 mol%), PPh_3 (18 mol%), Na_2CO_3 (2 M), benzene, reflux, 6 h.

Compound **3b** efficiently cyclises with 2,3,4,5-tetraphenylcyclopentadienone after a few minutes at 300°C to give 4-(2′,3′,4′,5′,6′-pentaphenyl)phenyl-6-methyl-2-pyrone **8** in excellent yield (>80%). These reactions are currently being investigated further.

Coupling of **2** *with alkenylmetals*: Many different types of alkenyl metals (Al, Zn, B, Zr, Mg and Sn) may be cross-coupled with aryl halides under Pd-catalysis. We focussed our attention on the Suzuki coupling of benzodioxaboroles **9** and boronic acids **10** with **2** (Scheme 4).

The bases generally used in Suzuki couplings are NaOEt and NaOH, but these were far too strong for the 2-pyrone unit to withstand due to the ease of basic hydrolysis. Indeed, rapid pyrone decomposition is observed in minutes. We found that using Na_2CO_3 (2 M), $Pd(OAc)_2$ (6 mol%) and PPh_3 as the ligand[11] gave the best yields of the products (Table 4). Higher concentrations of Pd catalyst (up to 20 mol%) were of no benefit, indeed this seemed to have a negative effect on both the reaction rate and product yields. It is well known that the alkenyl stereochemistry of the starting materials are conserved in such reactions and ^1H NMR coupling constants and quantitiative NOE studies[12] confirm the formation of the *E*-alkenylpyrones. For comparison we were also able to selectively reduce 4-phenylethynyl-6-methyl-2-pyrone to *Z*-4-phenylethenyl-6-methyl-2-pyrone **12** using Pd/C, H_2 and quinoline (87% yield).

Table 4 illustrates that higher yields are obtained from reactions where boronic acids were employed. This is advantageous, as the boronic acids are not air sensitive, unlike the benzodioxaboroles. Similar yields were also observed employing $Pd(PPh_3)_4$ as the catalyst.

In conclusion, we have found a variety of conditions for the Songashira coupling of terminal alkynes with 4-bromo-6-methyl-2-pyrone **2**, which we were able to extend to a modified Stille procedure. The Sonogashira method was more beneficial, in that the product purity was easier to maintain. A surprising result was the use of Pd/C as the most efficient catalyst for the majority of the alkynes—an unprecedented result. It was only when the alkyne possessed strongly electron-withdrawing substituents was the standard Pd(0) catalysts, $Pd(OAc)_2/PPh_3$ and $Pd(PPh_3)_4$, more effective. The synthesis of alkenylpyrones using Suzuki methodology and the employment of alkenylbenzodioxaboroles and alkenylboronic acids was successful. The more stable alkenylboronic acids proved more versatile and higher yielding. The correct choice of base was essential for such reactions, as strong bases tended to cause decomposition of the starting material. Our complete evaluation of other Pd-coupling procedures and important biological results of these 4-alkenyl/alkynyl-6-methyl-2-pyrones will be reported in full in due course.

Acknowledgements

We thank the EPSRC for a PhD studentship to L.R.M. and M.M.U. for funding. I.J.S.F. acknowledges the University of York for financial support in the form of an IRPF grant. We gratefully acknowledge a generous loan of palladium salts from Johnson Matthey PLC.

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8. Reaction of **2** and (phenylethynyl)zinc chloride in THF at 60°C under $Pd(PPh_3)_4$ catalysis has been reported to give the coupled product in 76% yield: Kalinin, V. N.; Shilova, O. S.; Okladnoi, D. S.; Schmidhamer, H. *Dokl. Chem. Engl. Transl.* **1996**, *351*, 276–278; *Dokl. Akad. Nauk*. **1996**, *351*, 67–69.
9. *Representative procedure*: A magnetically stirred mixture of **2** (1 mmol), alkyne (1.1 mmol), 10% Pd/C (20 mol%), PPh_3 (25 mol%) and CuI (4 mol%) in dry Et_3N (2.5 mL) and dry CH_3CN (1.5 mL) were heated at reflux under N_2 for 3 h. The mixture was cooled to room temperature and filtered over a pad of Celite, washed with CH_2Cl_2 and the filtrate concentrated in vacuo to give an oil. The coupled products were isolated by either direct recrystallisation or by extraction with hexane, followed by flash chromatography.
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11. *Representative procedure*: $Pd(OAc)_2$ (6 mol%), PPh_3 (18 mol%) and **2** (1 mmol) in benzene (2 mL) and aq. Na_2CO_3 (1 mL, 2 M) were magnetically stirred under N_2 for 0.5 h. To this was added a solution of the boronic acid (1.1 mmol) in EtOH (1 mL) and the solution was refluxed for 6 h, and then allowed to cool to room temperature. The excess boronic acids were oxidised with 30% H_2O_2 (0.1 mL) for 1 h. The mixture was extracted into hexane (2×10 mL) and the combined extracts washed with saturated aq. NaCl (2×10 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was purified by flash chromatography to give pale oils or solids.
12. For 4-phenylethenyl-6-methyl-2-pyrone, the *E*-isomer **11e** gave an 8% NOE to the methyl at the 6-position (C*H*=C*H*, $^3J = 16.48$ Hz) whereas the *Z*-isomer **12** gave a 2.5% NOE (C*H*=C*H*, $^3J = 12.09$).