Palladium-Catalysed Alkynylations of 2-Pyrone (Pyran-2-one) Halides

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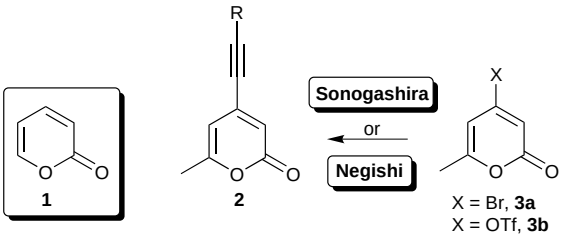
Abstract: The 2-pyrone sub-unit is found in a large number of natural products possessing broad-spectrum biological activity. As such, efficient synthetic methods are required to enable facile access to substituted 2-pyrone derivatives. Important conditions for the Sonogashira alkynylation of 4-bromo-6-methyl-2-pyrone (**3a**) have been developed, and compared against Negishi's methodology. The best conditions for Sonogashira alkynylation was found to be the use of Pd/C with added Ph_3P as the catalyst, in the presence of catalytic CuI, in a mixture of MeCN and Et_3N at reflux. Using Negishi's standard conditions, terminal alkynylzinc reagents, generated in situ from terminal alkynes with LDA or *n*-BuLi and subsequent reaction with anhydrous $ZnBr_2$, were reacted with **3a** at room temperature using $Pd(PPh_3)_4$ as the catalyst in THF.

Key words: palladium, Negishi reaction, Sonogashira reaction, 2-pyrones

The 2-pyrone ring system **1** (pyran-2-one), a 6-membered cyclic unsaturated ester, shares similar chemical and physical properties reminiscent of alkene and aromatic compounds (Scheme 1).[1] The core structure is biodiverse and found in many bacterial, microbial, plant, insect and animal systems.[2] 2-Pyrones demonstrate a vast array of bioactivity and exhibit antifungal, antibiotic, cytotoxic, neurotoxic and phytotoxic properties.[3] Very recently we have identified 4-alkynyl-6-methyl-2-pyrones **2** that inhibit the growth of A2780 human ovarian carcinoma and K562 human chronic myelogenous leukaemia cell lines at the micromolar level.[4] This promising bioactivity has encouraged us to identify useful synthetic protocols to these derivatives.

2-Pyrones also find a wide variety of synthetic applications,[5] in particular as a diene component in normal and inverse electron demand Diels–Alder reactions,[6] and as a precursor to other heterocyclic systems, such as 2-pyridones.[7] Despite the synthetic utility of 2-pyrones, the synthesis and construction of substituted derivatives can be fraught with difficulties, often requiring multi-step syntheses via acyclic precursors. Ring-opening and rearrangements usually thwart high yielding transformations, in some cases leaving the 2-pyrone ring impossible to regenerate. Direct substitutions onto the 2-pyrone ring, in particular organometallic couplings (Suzuki, Sonogashira, Stille and amination reactions), offer a versatile approach to the synthesis of a wide variety of 2-pyrones. Recent work by the likes of Cho,[8] Moreno-mañas and Pleixats,[9] Rossi[10] and our group[11] has highlighted the uses of halogenated 2-pyrones as substrates for organometallic cross-coupling reactions. Furthermore, we have reported the synthesis of bromo-2-pyrone tricarbonyliron complexes and their uses in the Suzuki reaction.[12] Such studies have begun to overcome the limitations associated with the chemistry of the 2-pyrone system.[13] In this paper[14] we report, in full, our investigations into the Sonogashira[15] alkynylation reactions of brominated 2-pyrone **3a** (Scheme 1). The reactions are compared and contrasted with Negishi's[16] recently reported alkynylation protocol.[17]



Scheme 1

We initially probed the Sonogashira reaction of **3a** using standard conditions (Table 1). The precatalyst, bis(triphenylphosphine)palladium(II) chloride $[(PPh_3)_2PdCl_2]$ is commonly employed in the Sonogashira reaction, however, this proved unsuccessful in acetonitrile, THF or DMF (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.[8] Historically it has been assumed that $(PPh_3)_2PdCl_2$ is reduced to $(PPh_3)_2Pd(0)$ in situ. Recent work by Amatore and Jutand has demonstrated that there is the possibility that the catalytic species produced from $(PPh_3)_2PdCl_2$ is anionic, namely $[(PPh_2)_2Pd(0)Cl]^-$.[18] Palladium black is formed very quickly in our reactions, suggesting that such a species is not formed under the conditions. Alternative methods for generating $(PPh_3)_2Pd(0)$ in situ proved superior. For example, use of $Pd(OAc)_2/PPh_3$ gave the coupled products in higher yields (entries 5–8, Table 1). Switching to tetrakis(triphenylphosphine)palladium(0) $[(PPh_3)_4Pd(0)]$ resulted in similar yields (entries 9–12, Table 1), whereas the commonly employed Pd(0) complex, $Pd_2dba_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) with added PPh_3 proved more efficient, albeit requiring a longer reaction time (entries 13–16, Table 1).

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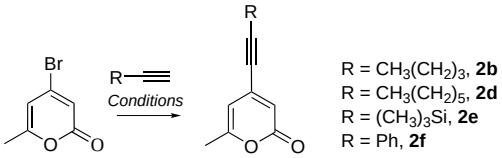
We turned our attention to the use of 10% palladium on charcoal with added PPh_3. The Pd-C (2 mol% Pd) and PPh_3 (2.5 mol%) catalyst combination clearly has a dramatic effect on the Sonogashira reaction of **3a** (entries 17–20, Table 1). We believe that this is the first time that such enhanced efficiency has been observed over standard Pd(0) based catalysts in the Sonogashira reaction. Recently it was reported that Pd-C is an efficient catalyst for the Sonogashira reaction of aryl halides with the proper choice of solvent.[19] Our conditions clearly allow Pd-C/PPh_3 to act as a superior catalyst system with respect to **3a**. The advantage of using this Pd(0) catalyst is that it is air stable and very convenient to use. We also altered the type of base and solvent in these reactions using Pd-C/PPh_3 (Table 2). It was found that THF in combination with *i*-Pr_2NEt (Hünig's base) was as effective as MeCN and Et_3N (entries 2 and, Table 2). Reactions conducted in Et_2O were lower yielding. Pyrrolidine functioned modestly as a base (entries 4 and 11, Table 2), whereas use of pyridine failed to facilitate cross-coupling (entries 3, 10 and 14, Table 2).

A number of terminal alkynes were cross-coupled with **3a** using the Pd-C/PPh_3 catalyst combination in Et_3N and MeCN at reflux (Table 3). Good to excellent yields were observed for the vast majority of these 2-pyrones. Poor yields were observed in reactions of **3a** with propargyl alcohol and propargyl acetate to give **2g** and **2l**, respectively. The structural complexity of 17α-ethynylesteradiol posed no problems towards cross-coupling, with **2p** isolated in 85% yield. Changing to the pseudohalide substrate triflate **3b**, synthesised in 81% yield using *N*-phenyltriflimide in the presence of potassium carbonate in THF at 60 °C,[20] improved the yields of the cross-coupled products in the Sonogashira reaction (**2a**–**c** and **2f**), and an enhanced rate of reaction was seen. Complete loss of **3b** was noted after only 1 hour!

Table 1 Sonogashira Reactions of **3a**[a]



Entry	Catalyst System	R	Yield (%)
1	$Pd(PPh_3)_2Cl_2/CuI/Et_3N$[b]	Me_3Si	0
2	as above	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]	Me_3Si	50
6	as above	Ph	43
7	as above	$Me(CH_2)_3$	48
8	as above	$Me(CH_2)_5$	27
9	$Pd(PPh_3)_4/CuI/Et_3N$[c]	Me_3Si	47
10	as above	Ph	32
11	as above	$Me(CH_2)_3$	52
12	as above	$Me(CH_2)_5$	53
13	$Pd_2dba_3{\cdot}CHCl_3/PPh_3/CuI/Et_3N$[d]	Me_3Si	69
14	as above	Ph	73
15	as above	$Me(CH_2)_3$	62
16	as above	$Me(CH_2)_5$	56
17	$Pd\text{-}C/PPh_3/CuI/Et_3N$[e]	Me_3Si	82
18	as above	Ph	74
19	as above	$Me(CH_2)_3$	77
20	as above	$Me(CH_2)_5$	81

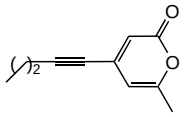
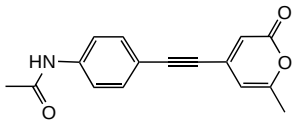
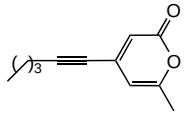
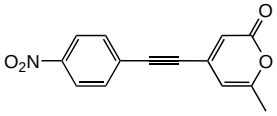
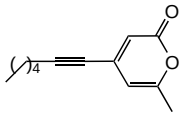
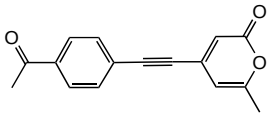
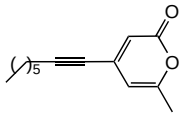
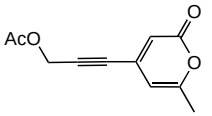
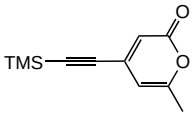
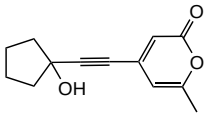
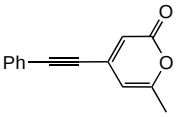
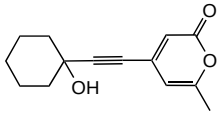
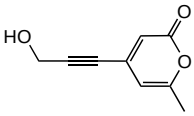
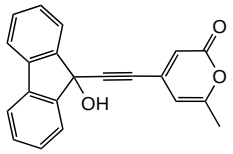
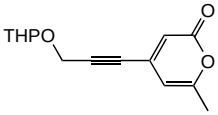
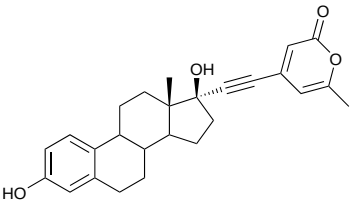
[a] All coupling reactions were conducted at reflux in a mixture of anhyd Et_3N and MeCN (2.5:1.5) with CuI (4 mol%) under N_2 for 3 h. MeCN was used unless stated.
[b] 6 mol% [Pd]-catalyst, 18 mol% PPh_3.
[c] 6 mol% [Pd]-catalyst.
[d] 2.5 mol% [Pd]-catalyst, 15 mol% PPh_3, 6–8 h.
[e] 10% Pd-C (2 mol% Pd), PPh_3 (2.5 mol%).

Table 2 Effect of Base and Solvent in Sonogashira Reactions of **3a**[a]

Entry	Solvent	Base	R	Yield (%)[b]
1	THF	Et_3N	Ph	88 (3)
2	THF	*i*-Pr_2NEt	Ph	91 (2)
3	THF	pyridine	Ph	0 (48)
4	THF	pyrrolidine	Ph	43 (48)
5	Et_2O	*i*-Pr_2NEt	Ph	68 (2)
6	MeCN	*i*-Pr_2NEt	Ph	95 (1)
7	DMF	*i*-Pr_2NEt	Ph	59 (2)
8	THF	Et_3N	Me	61 (48)
9	THF	*i*-Pr_2NEt	$Me(CH_2)_5$	98 (3)
10	THF	pyridine	$Me(CH_2)_5$	0 (48)
11	THF	pyrrolidine	$Me(CH_2)_5$	58 (5)
12	Et_2O	Et_3N	$Me(CH_2)_5$	23 (26)
13	Et_2O	*i*-Pr_2NEt	$Me(CH_2)_5$	36 (6)
14	Et_2O	pyridine	$Me(CH_2)_5$	0 (48)
15	MeCN	*i*-Pr_2NEt	$Me(CH_2)_5$	74 (3)

[a] All coupling reactions were conducted at reflux with the appropriate base and solvent (2.5:1.5), 10 % Pd/C (2 mol% Pd), PPh_3 (2.5 mol%), CuI (4 mol%), under N_2 or Ar.
[b] Refers to isolated yields. The reaction time is given in parenthesis.

Table 3 Sonogashira[a] and Negishi[b] Alkynylation of **3a** and **3b**

Coupled Product		Yield (%)[c]		Coupled Product		Yield (%)	
		Sonogashira	Negishi			Sonogashira	Negishi
	**2a**	72 (79)	79		**2i**	95	83
	**2b**	77 (75)	83		**2j**	95	64
	**2c**	79 (82)	72		**2k**	35	78
	**2d**	81 (68)	51		**2l**	0	40
	**2e**	82	91		**2m**	61	52[d]
	**2f**	74 (90)	81		**2n**	84	43[d]
	**2g**	5	20[d]		**2o**	90	85[d]
	**2h**	81	50		**2p**	85	92[d]

[a] *Sonogashira Conditions*: Anhyd Et_3N and anhyd MeCN (2.5:1.5), CuI (4 mol%), 10% Pd-C (2 mol% Pd), Ph_3P (2.5 mol%), under N_2 or argon for 3 h at reflux. Isolated yields after column chromatography.
[b] *Negishi Conditions*: *n*-BuLi or LDA, 78 to 0 °C, then $ZnBr_2$ added; followed by **3a**, $Pd(PPh_3)_4$ (5 mol%), THF, 25 25 °C.
[c] Isolated yields using triflate **3b** as the substrate are given in parenthesis.
[d] Excess LDA (2 or 3 equiv) and $ZnBr_2$ (2 or 3 equiv) were used with alkynes containing sensitive acidic functionalities.

A series of reactions of **3a** with alkynylzinc reagents using Negishi's protocol was undertaken. The alkynylzinc reagent was generated by reaction of the terminal alkyne with *n*-BuLi or LDA at –78 °C to 0 °C, followed by addition of $ZnBr_2$. The resultant alkynylzinc was added to **3a** and $Pd(PPh_3)_4$ (5 mol%), (THF, 25 °C, 4 h) to give the coupled products (Table 3). The yields fare well against the Sonogashira reaction. Notable improvements were seen for **2k** and **2l**. Being able to conduct reactions at room temperature is an advantage, although the alkynylzinc reagent has to be generated in situ prior to reaction with **3a**, which is the only limitation. Pleasingly, we were able to employ 17α-ethynylesteradiol as the alkyne component in these reactions using 3 equivalents of LDA and 3 equivalents of $ZnBr_2$.

In conclusion, important reactions conditions for the Sonogashira alkynylation of **3a** have been developed, which can be extended to other brominated 2-pyrones.[21] The 2-pyrone products will be useful for a number of reactions. Negishi's alkynylation protocol performs well in reactions of **3a** with terminal alkynes, containing varying de-

grees of structural complexity. These studies represent the first Negishi alkynylation reactions of halogenated 2-pyrones.

Terminal alkynes were purchased from Aldrich or Lancaster and redistilled or recrystallised. THF was dried over sodium-benzophenone ketyl (distilled prior to use). Anhyd CH_2Cl_2, Et_3N and MeCN were distilled over CaH_2. All reactions were conducted under an inert atmosphere of argon or N_2 on a Schlenk line. $Pd(PPh_3)_4$ was prepared prior to use from $Pd(OAc)_2$ and PPh_3 (1:5) in Et_2O, stirring at r.t. (1 h, in the dark!), then filtered through a sinter glass funnel (under N_2) to give $Pd(PPh_3)_4$ as a yellow solid. $Pd(OAc)_2$ was purchased from Aldrich or Strem. $PdCl_2$ was provided by Johnson Matthey as a gift. $(PPh_3)_2PdCl_2$ was prepared from $PdCl_2$ in refluxing DMSO and PPh_3 (2 equiv) using a known procedure.[22] 10% Pd-C was purchased from Lancaster. Compound **3a** was synthesised according to the literature procedure(s).[23] Melting points were recorded on an electrothermal IA9000 Digital Melting Point Apparatus and are uncorrected. TLC analysis was performed on Merck 5554 aluminum backed silica gel plates and compounds visualised by ultraviolet light (254 nm), phosphomolybdic acid solution (5% in EtOH), or 1% ninhydrin in EtOH. The relative proportion of solvents in mixed chromatography solvents refers to the volume/volume ratio. IR spectra were recorded on a ATI Mattson Genesis FT-IR spectrophotometer. Mass spectrometry was carried out using a Fisons Analytical (VG) Autospec instrument. High-resolution masses are within 5 ppm of theoretical values. ^{1}H NMR spectra were recorded at 270 MHz using a Jeol EX270 spectrometer or at 400 MHz using a Jeol ECX400 spectrometer; ^{13}C NMR spectra at 67.9 or 100.5 MHz; ^{19}F NMR spectra at 376.3 MHz. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), m (multiplet), br (broad).

6-Methyl-2-pyrone-4-trifluoromethanesulfonate (3b)

4-Hydroxy-6-methyl-2-pyrone (1 g, 7.9 mmol), K_2CO_3 (3.28 g, 23.8 mmol), and *N*-phenyltriflimide (2.97 g, 8.3 mmol) in anhyd THF (15 mL) were magnetically stirred at 60 °C for 4 h. The reaction mixture was cooled to r.t. and taken up in CH_2Cl_2 (100 mL), and washed with 5% aq NH_4Cl (2 × 25 mL), H_2O (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. Purification by column chromatography [petroleum ether (40–60 °C)–EtOAc, 1:1] gave the product as a pale yellow oil (1.66 g, 81%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.05 (1 H, s), 6.00 (1 H, s), 2.27 (3 H, s).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.4, 99.6, 102.4, 161.2, 162.4, 165.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –72.17 (3 F, s).

LRCI: *m*/*z* = 276 ([M + NH_4^+], 100), 259 ([MH^+], 15), 144, 127, 109, 72.

HRCI: *m*/*z* calcd for $C_7H_6F_3O_5S$: 258.9888; found: 258.9889.

Sonogashira Reaction of 3a with Terminal Alkynes; General Procedure

To a flame-dried flask under an atmosphere of N_2 or argon was added **3a** (1 mmol), the terminal alkyne (1 mmol), 10% Pd-C (20 mol%, 2 mol% based on Pd), PPh_3 (2.5 mol%) and CuI (4 mol%). Anhyd Et_3N (2.5 mL) and anhyd MeCN (1.5 mL) were added via cannula and the mixture was magnetically stirred and heated to reflux for 3 h. The mixture was cooled to r.t., and filtered through Celite, washed with CH_2Cl_2 and the filtrate was concentrated in vacuo to give an oil. The products were isolated by either direct recrystallisation or by extraction into hot hexane, followed by chromatography on silica gel using petroleum ether (40–60 °C)–EtOAc, 9:1) to provide the products as crystalline solids or viscous oils (Tables 1 and 2).

Negishi Reaction with 3a with Terminal Alkynes; General Procedure

To a solution of *i*-Pr_2NEt (1 mmol) in THF (5 mL) was added *n*-BuLi (1 mmol, 2.5 M solution in hexane) at 0 °C in a flame-dried flask under an atmosphere of N_2 or Ar. After 30 min, the terminal alkyne (1 mmol) in THF (1 mL) was added to the LDA solution via cannula at –78 °C, then stirred at this temperature for 0.5 h, and then treated with a solution of anhyd $ZnBr_2$ (1 mmol, dried at 60 °C under vacuum at ca. 1 mmHg for 8 h) in THF (2 mL), and warmed gradually to 0 °C over 0.5 h. After this time, **3a** (1 mmol) and $Pd(PPh_3)_4$ were added to the reaction mixture at 0 °C. The mixture was allowed to warm to r.t. (ca. 25 °C) and stirring was continued for 2–4 h. The mixture was quenched with aq NH_4Cl, extracted with EtOAc, which was washed with aq $NaHCO_3$ and then brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was carried out as above (Table 3).

4-Pentynyl-6-methyl-2-pyrone (2a)

Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 1:1) to give a dark oil.

IR (neat): 3096, 2934, 2224, 1729 (C=O), 1639, 1540, 1445, 1313, 1135, 847 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.14 (1 H, s), 5.93 (1 H, s), 2.40 (2 H, t, ^3J = 7.3 Hz), 2.22 (3 H, s), 1.62 (2 H, sx, ^3J = 7.3 Hz), 0.93 (3 H, t, ^3J = 7.3 Hz).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 162.2, 161.5, 139.7, 113.9, 105.7, 101.0, 77.45, 21.4, 21.3, 19.6, 13.2.

LREI *m*/*z* = 176 ([M^+]), 161 ([$M^+ - CH_3$]), 148 ([M^+ – C≡O]), 133 ([$M^+ - C_3H_7$]), 119, 105, 93, 77, 65, 51, 43.

LRCI: *m*/*z* = 177 ([MH^+]), 100).

HRCI: *m*/*z* calcd for $C_{11}H_{13}O_2$: 177.0915; found: 177.0912.

4-Hexynyl-6-methyl-2-pyrone (2b)

Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 1:1) to give a dark oil.

IR (neat): 3097, 2934, 2872, 2230, 1738 (C = O), 1639, 1540, 1445, 1313, 1135, 849 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.13 (1 H, s), 5.93 (1 H, s), 2.43 (2 H, t, ^3J = 7.0 Hz), 2.20 (3 H, s), 1.36–1.62 (4 H, m), 0.93 (3 H, t, ^3J = 7.3 Hz).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 162.2, 161.5, 139.7, 113.9, 105.7, 101.3, 77.3, 30.0, 21.8, 19.6, 19.1, 13.3.

LREI: *m*/*z* = 190 ([M^+]), 175 ([$M^+ - CH_3$]), 161 ([$M^+ - C_2H_5$]), 147 ([$M^+ - C_3H_7$]), 133 ([$M^+ - C_4H_9$]), 119, 105, 93, 73, 65.

LRCI: *m*/*z* = 191 ([MH^+], 100).

HRCI: *m*/*z* calcd for $C_{12}H_{14}O_2$: 191.1072; found: 191.1070.

4-Heptynyl-6-methyl-2-pyrone (2c)

Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 2:3) to give a dark oil.

IR (neat): 3095, 2929, 2228, 1730 (C = O), 1639, 1544, 1445, 1313, 1136, 849 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.14 (1 H, s), 5.92 (1 H, s), 2.41 (2 H, t, ^3J = 7.0 Hz), 2.21 (s, 3 H), 1.60 (2 H, m), 1.30–1.45 (4 H, m), 0.92 (3 H, t, ^3J = 7.0 Hz).

^{13}C NMR (68 MHz, CD_2Cl_2): δ = 162.2, 140.1, 114.9, 114.3, 105.9, 101.6, 77.7, 31.4, 28.2, 22.5, 20.0, 19.9, 14.0.

LRCI: *m*/*z* 205 ([MH$^+$], 100).

HRCI: *m*/*z* calcd for $C_{13}H_{17}O_2$: 205.1228; found: 205.1227.

4-Octynyl-6-methyl-2-pyrone (2d)
Purified by extraction into hexane, followed by chromatography on silica gel (Et_2O–hexane, 2:3) to give a dark oil.

IR (neat): 3097, 2930, 2859, 2230, 1733 (C=O), 1640, 1542, 1444, 1313, 1135, 849 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.12 (1 H, s), 5.91 (1 H, s), 2.40 (2 H, t, ^3J = 6.8), 1.58 (2 H, qn, ^3J = 7.6 Hz), 1.26–1.46 (m, 6 H), 0.89 (3 H, t, ^3J = 6.8 Hz).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 162.2, 140.0, 114.4, 105.9, 101.6, 77.7, 31.6, 28.9, 28.5, 22.9, 20.0, 19.9, 14.2.

LREI: *m*/*z* = 218 ([M$^+$]), 203 ([M$^+$ – CH_3]), 175 ([M$^+$ – C_3H_7]), 161 ([M$^+$ – C_4H_9]), 148, 135, 120, 105, 91, 77, 65, 55, 43 (100).

LRCI: *m*/*z* = 219 ([MH$^+$], 100), 205.

HRCI: *m*/*z* calcd for $C_{14}H_{19}O_2$: 219.1385; found: 219.1384.

4-(Trimethylsilylethynyl)-6-methyl-2-pyrone (2e)
Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 1:1) to give a dark oil.

IR (neat): 3095, 2961, 2900, 2112, 1745 (C=O), 1638, 1538, 1312, 1252, 964, 846 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.11 (1 H, s), 5.92 (1 H, s), 2.21 (3 H, s), 0.25 (9 H, s).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 161.9, 138.5, 115.1, 114.7, 108.3, 105.3, 100.1, 19.7, –0.6.

LREI: = *m*/*z* 206 ([M$^+$]), 191 ([M$^+$ – CH_3]), 163, 84, 75, 49 (100).

LRCI: *m*/*z* = 207 [M$^+$+1] (100), 191, 178, 90.

HRCI: *m*/*z* calcd for $C_{11}H_{15}O_2Si$: 207.0841; found: 207.0838.

4-(Phenylethynyl)-6-methyl-2-pyrone (2f)
Isolated by extraction into hot hexane and recrystallised to give a pale brown solid; mp 85–86 °C.

IR (KBr): 3086, 2203, 1723 (C = O), 1705, 1642, 1535, 1439, 1310, 1135, 956, 840, 763 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.38–7.59 (5 H, m), 6.30 (1 H, s), 6.05 (1 H, s), 2.26 (3 H, s).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 162.1, 161.9, 138.9, 132.1, 129.9, 128.6, 121.3, 114.5, 105.3, 98.5, 85.4, 19.8.

LREI: *m*/*z* = 210 ([M$^+$]), 195 ([M$^+$ – CH_3]), 182 ([M$^+$ – C≡O]), 153, 139 (100), 127, 113, 87, 69, 51.

LRCI: *m*/*z* = 211 ([MH$^+$], 100), 182.

HRCI: *m*/*z* calcd for $C_{14}H_{11}O_2$: 211.0759; found: 211.0765.

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.80. Found: C, 79.65; H, 4.98.

4-(3′-Hydroxyprop-2′-ynyl)-6-methyl-2-pyrone (2g)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a light yellow solid; mp 119–121 °C.

IR (CH_2Cl_2): 3443 (br, OH), 1718 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (1 H, d, ^4J = 2.1 Hz), 5.53 (1 H, d, ^4J = 2.1 Hz), 4.66 (2 H, s), 2.63 (1 H, s), 2.22 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 56.3, 75.9, 77.3, 88.9, 100.2, 162.5, 164.5, 169.1.

LRCI: *m*/*z* = 207 ([MH$^+$], 100), 149, 142.

HRCI: *m*/*z* calcd for $C_{11}H_{11}O_4$: 207.0657; found: 207.0660.

6-Methyl-4-[3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl-2-pyrone (2h)
Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 1:1) to give a dark oil.

IR (neat): 3097, 2943, 2871, 2231, 1727 (C=O), 1640, 1542, 1443, 1388, 1314, 1238, 1122, 1029, 902, 870 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.14 (1 H, s), 5.89 (1 H, s), 4.74 (1 H, t, ^3J = 3.5 Hz), 4.40 (2 H, d, ^3J = 3.5 Hz), 3.78 (1 H, m), 3.49 (1 H, m), 2.16 (3 H, s), 1.40–1.85 (6 H, m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 161.9, 161.8, 138.3, 114.7, 105.1, 97.1, 95.1, 81.6, 61.8, 54.2, 30.0, 25.1, 19.6, 18.7.

LRCI: *m*/*z* = 249 ([MH$^+$], 25), 211, 165, 102. 85 (100).

HRCI: *m*/*z* calcd for $C_{14}H_{17}O_4$: 249.1126; found: 249.1123.

***N*-[4-(6-Methyl-2-oxo-2*H*-pyran-4-ylethynyl)phenyl]acetamide (2i)**
Purified by extraction into hot hexane, followed by chromatography on silica gel (Et_2O–hexane, 1:1) to give a yellow solid; mp 224–225 °C.

IR (CH_2Cl_2): 1726 (C=O), 1706 (C=O), 1511 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) 7.51–7.66 (5 H, br m), 6.32 (1 H, s), 5.75 (1 H, s), 3.32 (3 H, s), 2.47 (3 H, s).

LRCI: *m*/*z* = 279 ([M + NH_4^+], 100), 268 ([MH$^+$], 62), 210, 102.

HRCI: *m*/*z* calcd for $C_{16}H_{14}NO_3$: 268.0975; found: 268.0974.

4-(4′-Nitrophenylethynyl)-6-methyl-2-pyrone (2j)
Purified directly by chromatography on silica gel ($CHCl_3$), followed by recrystallisation from MeCN; mp 189–191 °C (dec.).

IR (neat): 3099, 2210, 1721 (C=O), 1644, 1590, 1538, 1512, 1340, 1213, 1102, 958, 845, 749 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.27 (2 H, d, ^3J = 8.8), 7.70 (2 H, d, ^3J = 8.8), 6.36 (s, 1 H), 6.07 (s, 1 H), 2.28 (s, 3 H).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 162.5, 161.6, 148.0, 137.6, 132.9, 127.8, 123.7, 115.5, 104.8, 95.2, 89.3, 19.9.

LREI: *m*/*z* = 255 ([M$^+$]), 227 ([M$^+$ – C≡O]), 197, 181, 152, 137, 115, 69, 43.

LRCI: *m*/*z* = 256 ([MH$^+$], 28), 226 (100).

HRCI: *m*/*z* calcd for $C_{14}H_{10}NO_4$: 256.0609; found: 256.0605.

Anal. Calcd for $C_{14}H_{10}NO_4$: C, 65.88; H, 3.53. Found: C, 65.64; H, 3.62.

4-(4′-Acetylphenylethynyl)-6-methyl-2-pyrone (2k)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a pale yellow solid; mp 155–157 °C.

IR (KBr): 3037, 1716 (C=O), 1680 (C=O), 1628, 1536 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.97 (2 H, d, ^3J = 8.4 Hz), 7.62 (2 H, d, ^3J = 8.4 Hz), 6.33 (s, 1 H), 6.07 (s, 1 H), 2.63 (2 H, s), 2.27 (3 H, s).

^{13}C NMR (68 MHz, $CDCl_3$): 196.9, 162.2, 161.8, 138.2, 137.5, 132.2, 128.3, 125.8, 115.0, 105.0, 96.9, 87.8, 26.6, 19.9.

LREI: *m*/*z* = 252 ([M$^+$]), 237 ([M$^+$ – CH_3]), 209, 181, 159, 138, 123, 103, 89, 71, 57 (100), 41.

LRCI: *m*/*z* 253 ([MH$^+$], 100).

HRCI: *m*/*z* calcd for $C_{16}H_{13}O_3$: 253.0864; found: 253.0863.

4-(3′-Acetoxy-prop-2′-ynyl)-6-methyl-2-pyrone (2l)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a pale yellow oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.24 (1 H, s), 5.96 (1 H, s), 4.88 (2 H, s), 2.26 (3 H, s), 2.14 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 20.6, 52.0, 81.7, 91.9, 104.5, 114.9, 137.3, 161.4, 161.8, 169.5.

LRCI: *m*/*z* = 207 ([MH^+], 100), 149, 142.

HRCI: *m*/*z* calcd for $C_{11}H_{11}O_4$: 207.0657; found: 207.0660.

4-(Ethynylcyclopentan-1′-ol)-6-methyl-2-pyrone (2m)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a light brown viscous oil.

IR (CH_2Cl_2): 3599 (s, OH), 1727 (C=O), 1637 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.20 (1 H, s), 5.96 (1 H, s), 3.08 (1 H, br), 2.23 (3 H, s), 1.68–2.02 (8 H, br m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.7, 23.4, 42.1, 74.4, 79.2, 103.3, 105.6, 114.4, 139.1, 161.9, 162.5.

LRCI: *m*/*z* = 219 ([MH^+], 100).

HRCI: *m*/*z* calcd for $C_{13}H_{15}O_3$: 219.1021; found: 219.1021.

4-(Ethynylcyclohexan-1′-ol)-6-methyl-2-pyrone (2n)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a viscous yellow oil.

IR (Nujol): 1731, 1623, 1551, 1298, 1068 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.20 (1 H, s), 5.97 (1 H, s), 3.42 (1 H, br), 2.23 (3 H, s), 1.25–2.02 (10 H, br m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.7, 23.1, 24.9, 39.3, 68.9, 80.3, 103.0, 105.7, 114.5, 139.0, 162.0, 162.4.

LRCI: *m*/*z* = 233 ([MH^+], 100).

HRCI: *m*/*z* calcd for $C_{14}H_{17}O_3$: 233.1177; found: 233.1175.

4-(Ethynyl-9*H*-fluorenyl-9′-ol)-6-methyl-2-pyrone (2o)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a yellow solid; mp 145–147 °C.

IR (CH_2Cl_2): 3425, 1727 (C=O), 1693, 1625 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.60 (2 H, d, ^3J = 7.8 Hz), 7.52 (2 H, d, ^3J = 7.8 Hz), 7.23–7.32 (4 H, m), 5.95 (1 H, s), 5.77 (1 H, s), 3.80 (1 H, br), 2.01 (3 H, s), 1.25–2.02 (10 H, br m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.6, 74.7, 78.5, 99.5, 105.4, 114.8, 120.2, 124.4, 128.5, 129.9, 138.4, 139.0, 146.1, 161.8, 162.2.

LRCI: *m*/*z* = 315 ([MH^+], 100).

HRCI: *m*/*z* calcd for $C_{21}H_{15}O_3$: 315.1021; found: 315.1021.

4-(17α-Ethynylestradiol)-6-methyl-2-pyrone (2p)
Purified by chromatography on silica gel (EtOAc–hexane, 1:1) to give a light brown soild; mp 112–114 °C.

IR (Nujol): 3440, 1728 (C=O), 1693, 1142 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.13 (1 H, d, ^3J = 5.6 Hz), 6.66 (1 H, d, ^3J = 5.6 Hz), 6.58 (1 H, s), 6.23 (1 H, s), 5.97 (1 H, s), 5.45 (1 H, br), 4.11 (1 H, m), 2.82 (2 H, br m), 2.41 (1 H, br s), 2.23 (3 H, br s), 1.25–1.95 (12 H, br m), 0.98 (3 H, s).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.8, 19.8, 26.3, 27.8, 29.7, 33.7, 39.0, 39.3, 44.0, 47.9, 50.1, 81.0, 82.4, 103.2, 105.6, 112.5, 114.6, 115.3, 126.6, 132.0, 138.4, 139.2, 153.7, 162.1, 162.5.

LRCI: *m*/*z* = 405 ([MH^+], 4), 263, 127 (100).

HRCI: *m*/*z* calcd for $C_{26}H_{29}O_4$: 405.2066; found: 405.2066.

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