Palladium-catalysed heteroannulation with acetylenic compounds: synthesis of benzofurans[1]

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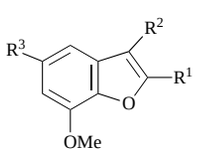
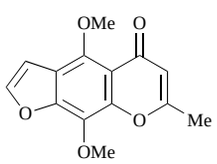
A detailed study of the heteroannulation of *o*-iodophenol with acetylenic substrates through palladium–copper catalysis leading to the synthesis of the 2-substituted benzofurans 21–29 is reported. An acylic compound 30 has been isolated and proved to be an intermediate in the synthesis of the benzofurans. Some of the benzofurans have been transformed into biologically active compounds.

Benzo[*b*]furan derivatives are of considerable interest because of both their widespread occurrence among natural products and their physiological properties.[2–3] Notable amongst these are compounds: machicendiol[4] **1**, a constituent of the extracts of *Machilus glaucescens* (Lauraceae), used in the treatment of asthma, rheumatism and ulcers; the active component, 5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-benzo[*b*]furancarbaldehyde[5] **2** of the aqueous extracts of *S. miltiorrhiza* Bunge 'Danshen', widely used in China to treat acute myocardiac infarction and angina pectoris; khellin **3**, a benzofuran derivative effective against bronchial asthma;[6] and tremetone **4**, hydroxytremetone **5**, toxol **6** and dehydrotremetone **7** isolated from *Eupatorium utricaefolium* and *Aplopappus heterophyllus*, known to cause trembles in cattle and milk sickness in humans.[7]



1 R^1 = 3',4'-methylenedioxyphenyl
R^2 = H, R^3 = $CH(OH)CH_2CH_2OH$



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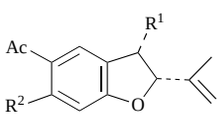
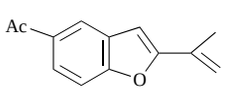
2 R^1 = 3'-methoxy-4'-hydroxyphenyl
R^2 = CHO, R^3 = $(CH_2)_3OH$



4 R^1 = R^2 = H
5 R^1 = H, R^2 = OH
6 R^1 = OH, R^2 = H



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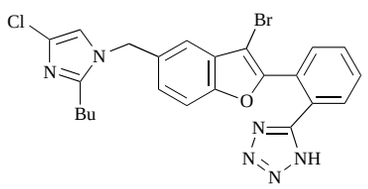
Besides these, benzofuran-containing structures have been found amongst naturally occurring furocoumarins, *e.g.* psoralen and methoxalen obtained from the seeds of *Amni majus* L and used for the treatment of psoriasis and other dermal diseases,[8] oroselol isolated from *Nardostachys jatamansi*, a herb growing at great elevation up to 1700 ft in the Himalayas,[9] usnic acid, a common lichen metabolite showing inhibitory effect on Gram positive bacteria,[10] pterocarpans,[11] natural defence agents called phytoalexin in plants, and kadsurenone, a potent and specific platelet activating factor (PAF) antagonist.[12] Recently, a group of novel benzofurans **8** which are antagonists of angiotenson II has been described[13] and their structure–activity relationship studied.[14]

Because of their occurrence as natural products and their



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biological activities, various classical methods have been developed over the years for elaborating the benzofuran structure and these have been amply reviewed.[2,3] More recently progress in this area have been made through the development of methods involving (1) ketene intermediates,[15] (2) cycloadditions,[12] (3) titanium chloride–zinc reagents,[16] (4) a modified Castro reaction[17] using acetylenic substrates with Cu_2O in pyridine[18,19] or (5) Bu^tOCu,[20] and (6) an anionic cycloaddition–thermal cycloreversion strategy.[21] Thus, a number of syntheses of natural products containing the benzofuran nucleus have been reported.[22]

Recent efforts, however, have centred around the use of palladium catalysts for carbon–carbon bond formation[23] and carbon–heteroatom bond formation.[24] The palladium-catalysed syntheses of substituted benzofurans have been reported involving the cyclisation of 2-allylphenols,[25] the reaction between (1-ethoxyalk-1-en-2-yl)boranes and 2-iodophenol and subsequent acidic cyclisation,[26] and palladium-promoted cyclisation of *o*-iodoaryl allyl ethers.[27] The palladium-catalysed reactions of *o*-iodophenols with 1,3-dienes and 1,2-dienes leading to the substituted benzofurans have also been accomplished.[28] Dyker[29] has reported the synthesis of substituted benzofurans from the palladium-catalysed cross-coupling between *o*-iodomethoxybenzenes and bromoolefins. The cyclocarbonylation of 3-furylallyl acetates in the presence of palladium catalysts led to the acetoxybenzofurans.[30] The functionalisation of pre-formed benzofurans under palladium-catalysed conditions has also been reported.[31]

Acetylenic substrates have played a very significant role in palladium-catalysed reactions for carbon–carbon bond formation leading to cyclic and polycyclic structures,[32] macrocycles,[33] fulvenes,[34] flavones and chromones,[35] γ-butyrolactones,[36] indoles,[37] quinoline derivatives,[38] phthalides[39] and isocoumarins.[40] For the synthesis of 2-substituted benzofurans, Buckle and Rockell[41] reported a two-step process involving a palladium-catalysed arylation of (2-methoxyphenyl)ethynes. The heteroannulation of *o*-iodophenols with acetylenic substrates containing a terminal acetylenic group leading to 2-substituted benzofurans have been reported by several groups of investigators including ours,[1,42–45] whereas the palladium-catalysed cyclisation of *o*-iodoaryl prop-2-ynyl ether led to the 3-substituted benzofurans.[46] A somewhat different approach

Table 1 Palladium-catalysed heteroannulation of the acetylenic compounds **10**–**18** leading to the benzofurans **21**–**29**

Entry	Alkynes (R)	Catalysts	Solvent/Base	Other reagents	Conditions *T*/°C; *t*/h	Products	Yields (%)
1	**10** (Ph)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**21**	77
2	**11** (C_6H_4Cl-*m*)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**22**	61
3	**12** (CH_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**23**	68
4	**13** (CMe_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 6	**24**	55
5	**13** (CMe_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**24**	75
6	**13** (CMe_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–NaOAc	Bu_4NCl	RT; 12	**24** + **30**	38 (3:7)
7	**13** (CMe_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–NaOAc	Bu_4NCl	RT; 24	**24** + **30**	68 (7:3)
8	**13** (CMe_2OH)	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–NaOAc	Bu_4NCl	50; 6	**24**	50
9	**13** (CMe_2OH)	$Pd(OAc)_2$, CuI	DMF–Et_3N	—	60; 6	**24**	20
10	**13** (CMe_2OH)	$Pd(OAc)_2$, CuI	DMF–Et_3N	Ph_3P	60; 6	—	—
11	**14** (CH_2OTHP)	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N	—	RT; 24	**25** + **23**	72 (3:1)
12	**15** [CH(OH)CH=CHMe]	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**26**	88
13	**16** [CH(OH)Ph]	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	80; 24	**27**	67
14	**16** [CH(OH)Ph]	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	60; 16	**27**	54
15	**16** [CH(OH)Ph]	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N	—	60; 16	**27**	48
16	**16** [CH(OH)Ph]	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N	—	RT; 24	**27**	27
17	**17** [$CH(OH)C_6H_4Me$-*o*]	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N	—	60; 16	**28**	56
18	**17** [$CH(OH)C_6H_4Me$-*o*]	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	80; 24	**28**	72
19	**18** [$CH(OH)C_6H_4OMe$-*p*]	$Pd(Ph_3P)_2Cl_2$, CuI	DMF–Et_3N	—	80; 24	**29**	64
20	**19** (CO_2Me)	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N or NaOAc or $NaHCO_3$ in MeCN	—	RT; 24	—	—
21	**20** (H)	$Pd(Ph_3P)_2Cl_2$, CuI	Et_3N	—	RT; 24	—	—

has been the palladium-catalysed carbonylation of 2-acetylenic phenols leading to substituted benzofurans.[47] Similarly, the palladium-catalysed arylation of alkyl or aryl acetylenic phenols in the presence of butyllithium led to 2-alkylidenebenzofurans.[48] Recently, a benzofuran natural product, ailanthoidal, was synthesised by the palladium-catalysed coupling of an aryl-substituted acetylene and a mesylated *o*-iodophenol.[49] The synthesis of 2,3-disubstituted benzofurans by palladium-catalysed annulation of internal alkynes has also been reported.[50]

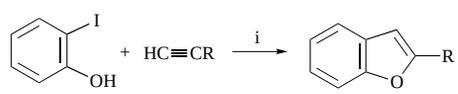
Results and discussion

In our pursuit of the development of various heterocyclic structures through palladium-catalysed reactions, we have developed[1] a general and convenient method for the heteroannulation of acetylenic compounds leading to benzofuran derivatives and here we report a detailed study of this. A mixture of *o*-iodophenol **9** and an alkyne **10**–**18** with a terminal acetylenic function, when heated in the presence of a palladium catalyst, copper(I) iodide and a base in dimethylformamide, gave the 2-substituted benzofurans **21**–**29** in excellent yields (Table 1; see Scheme 1).

The reactions were usually carried out for 16 h at 60 °C, lower temperatures leading to poor yields (entry 15 *vs*. 16). The reactions when carried out in DMF at room temperature in the presence of tetrabutylammonium chloride (PTC), gave a mixture of the cyclic product (benzofuran), **24** and the corresponding acyclic product **30** (entries 6 and 7), the overall yield and the proportion of the cyclic product increasing with time. At a higher temperature (50 °C) for 6 h (entry 8), the cyclic product **24** was formed exclusively. This indicated that the acyclic product **30** was an intermediate in the formation of the benzofuran **24**. However, with several aryl acetylenic carbinols (entries 13, 18 and 19), a slightly higher temperature (80 °C) and a longer reaction period (24 h) were required to derive the optimum yields.

Catalysts

Bis(triphenylphosphine)palladium(II) chloride (2–3.5 mol%) was found to be the catalyst of choice with, in all cases, cuprous iodide (3–5 mol%) needed as a co-catalyst. This catalyst system was originally suggested by Hagihara and coworkers[51] and has been effectively utilised by us in the synthesis of substituted alkynes from the reaction of acetylene



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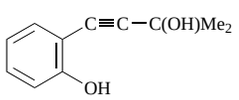
	R	
10	Ph	**21**
11	C_6H_4Cl-*m*	**22**
12	CH_2OH	**23**
13	CMe_2OH	**24**
14	CH_2OTHP	**25**
15	CH(OH)CH=CHMe	**26**
16	CH(OH)Ph	**27**
17	$CH(OH)C_6H_4Me$-*o*	**28**
18	$CH(OH)C_6H_4OMe$-*p*	**29**
19	CO_2Me	–
20	H	–



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Scheme 1 *Reagents and conditions*: i, $Pd(Ph_3P)_2Cl_2$ (2–3.5 mol%), CuI (3–5 mol%), DMF, Et_3N

gas with aryl iodides.[52] Other investigators have also used the $(Ph_3P)_2PdCl_2$–$Cu^{I}I$, catalyst–co-catalyst system for the condensation of aryl or heteroaryl halides with alkynes.[53] Use of other catalysts, *e.g.* $Pd(OAc)_2$ led to poorer yield (entry 9 *vs*. 4) whereas addition of triphenylphosphine which is known to improve yields in certain palladium–catalysed reactions[54] was found to suppress completely formation of the benzofuran (entry 10).

Solvents and bases

Dimethylformamide (DMF) was found to be the best solvent for the reactions we have studied because of its excellent ability to solubilise all the starting materials and the catalysts. Triethylamine was used as a base (2 equiv.; entries 1–5, 9, 10, 12–14, 18–19). Use of Et_3N as a base as well as a solvent was also tried and although the work-up was easier, giving rise to somewhat cleaner products, yields were somewhat lower (entry 14 *vs*. 15 and entry 18 *vs*. 17). In a few cases, NaOAc was used as a base with PTC (Bu_4NCl) (entries 6–8), where the acyclic products could be isolated if the reactions were carried out at room temperature (entries 6 and 7).

Table 2 ^{1}H NMR and UV spectra of 2-substituted benzofurans

Compounds	3-H	λ_{max}/nm
2-Phenylbenzofuran **21**	7.06 (s)	316, 308, 261, 226
2-(*m*-Chlorophenyl)benzofuran **22**	7.10 (s)	319, 304, 232
2-Hydroxymethylbenzofuran **23**	6.68 (s)	283, 277, 247
2-(1′-Hydroxyisopropyl)benzofuran **24**	6.60 (s)	283, 276, 247
2-(Tetrahydropyranyloxymethyl)benzofuran **25**	6.63 (s)	284, 277, 248
2-Isopropenylbenzofuran **33**	6.68	302, 294, 283
2-(1′-Hydroxybut-2-enyl)benzofuran **26**	6.68 (s)	284, 277, 249
Benzofuran-2-yl(phenyl)methanol **27**	6.52 (s)	284, 277, 249
o-Methylphenyl(benzofuran-2-yl)methanol **28**	6.41 (s)	285, 278, 250
p-Methoxyphenyl(benzofuran-2-yl)methanol **29**	6.46 (s)	285, 278, 251

Nature of substituents in the alkynes

For the synthesis of benzofurans, we have utilised alkynes with a terminal acetylenic group substituted at the other carbon atom with an alkyl or aryl group equally satisfactorily. The presence of other functional groups *e.g.* hydroxy (entries 3, 5, 12, 13, 17–19), vinyl (entry 12), aromatic (entries 13, 17–19), and pyranyl (entry 11) did not impede the reactions. When vinyl and acetylenic functional groups were present simultaneously in the substrate, the palladium-catalysed reaction took place at the acetylenic functional group only (entry 12). However, the reaction could not be carried out with a methoxycarbonyl substituent (*e.g.* propiolic ester; entry 20). Triethylamine when used as a base at room temperature for 24 h gave only polymerisation. Use of sodium hydrogen carbonate or sodium acetate as a base failed to yield any product. Similarly, the reaction of acetylene gas with *o*-iodophenol in triethylamine in a balloon in the presence of palladium–copper catalyst (entry 21) failed to yield the parent benzofuran.

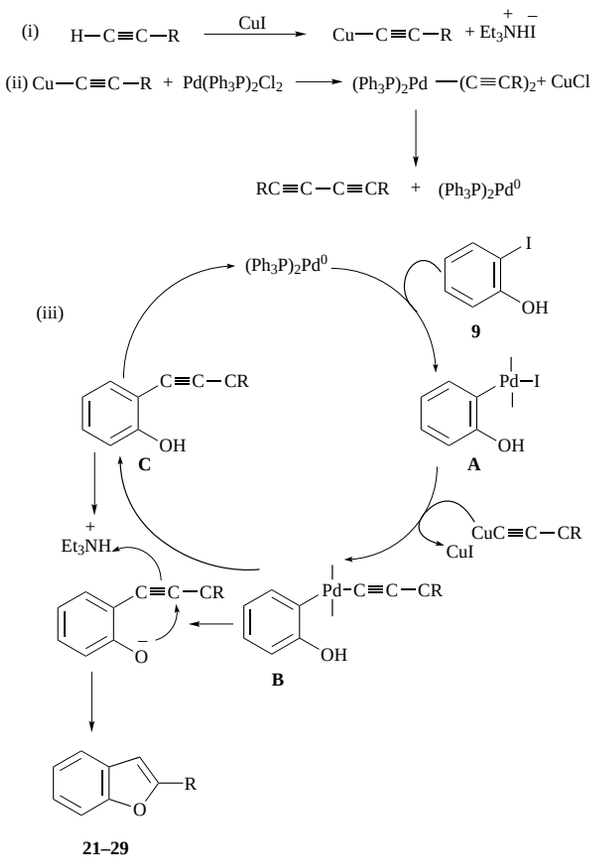
Nature of the products

The palladium-catalysed condensation of *o*-iodophenol with various acetylenic substrates have yielded a number of 2-substituted benzofurans in good to excellent yields (Table 1). All the products were stable at room temperature and could be handled and stored without any further precaution. The products were well characterised by spectroscopic data (IR, UV and ^{1}H NMR) and satisfactory elemental analyses. Appearance of a singlet near δ 6.6 or 7.1 in the ^{1}H NMR spectra was assigned to the 3-H of 2-alkyl or 2-aryl substituted benzofurans respectively (Table 2). Also, in their UV spectra all the compounds synthesized showed absorption of the type λ_{max}/nm 315, 303 and 225 for 2-aryl substituted benzofurans **21**, **22** and λ_{max}/nm 283, 275 and 247 for 2-alkyl substituted benzofurans **23**–**29** (Table 2).

Mechanism of the reaction

A mechanism for the formation of 2-substituted benzofurans by a single-step palladium-catalysed reaction of *o*-iodophenol with alkynes having a terminal acetylenic group is illustrated in Scheme 2.

The formation of Pd^0 from the interaction of bis(triphenylphosphine)palladium(II) chloride and cuprous acetylide as shown in step (ii) was proposed by Hagihara and co-workers.[51] We have found evidence in favour of this from our recent work on the dimerisation of monosubstituted alkynes to 1,4-disubstituted 1,3-diynes by palladium–copper catalysis.[55] Oxidative addition of *o*-iodophenol to a Pd^0 complex gives a σ-arylpalladium(II) complex (**A**) which then trans-metallates with cuprous acetylide to generate the arylalkynylpalladium(II) species (**B**). This on reductive elimination of Pd^0 then affords acyclic products, *e.g.* 2-alkynylphenols (**C**). The latter on cyclisation in the presence of triethylamine where the phenoxide ion made an attack on the triple bond resulted in the formation of the benzofurans. Such cyclisations are favoured reactions[56] and are in accord with the known ability of 2-alkynylphenols to cyclise under alkaline conditions.[57] This was confirmed by the



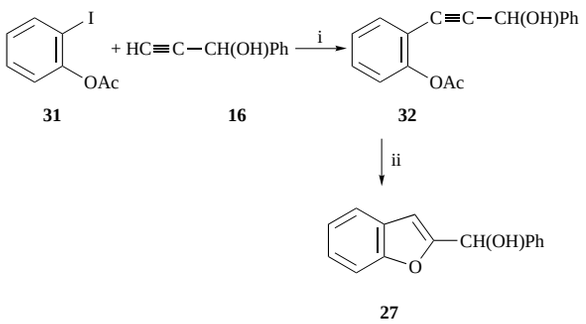
Scheme 2

conversion of compound **30** into 2-(1′-hydroxyisopropyl)-benzofuran **24** by treatment with triethylamine at 60 °C for 6 h. Further evidence in favour of the proposed mechanism was obtained by base-catalysed cyclisation of the acyclic compound **32** (synthesised by palladium-catalysed coupling of *o*-acetoxyiodobenzene **31** with 1-phenylprop-2-yn-1-ol **16**) into benzofuran-2-yl(phenyl)methanol **27** (Scheme 3).

Conclusions

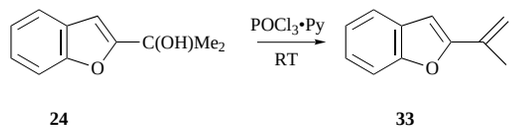
Some of the benzofurans we have synthesised have potential as intermediates of naturally occurring compounds or useful biologically active compounds. Thus, 2-(2′-hydroxyisopropyl)-benzofuran **24** was dehydrated to 2-isopropenylbenzofuran[58] **33** (Scheme 4) which constitutes the skeleton of dehydrotremetone and other natural products as well as useful substrates in Diels–Alder reactions.

Similarly, 2-(benzofuryl)arylcarbinols **27**, **29** may be oxidised with active manganese dioxide in dichloromethane at room temperature to 2-aroylbenzofurans, **34**, **35**, which are known to be biologically active.[59] Also, 2-hydroxymethylbenzofuran may be oxidised under Jones conditions to give benzofuran-2-carboxylic acid[60] **36** (Scheme 5).



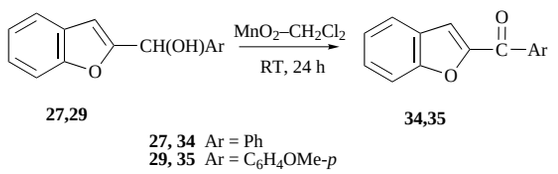
31 **16** **32** **27**

Scheme 3 *Reagents and conditions*: i, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, RT, 24 h; ii, NaOEt in EtOH, reflux, 4 h



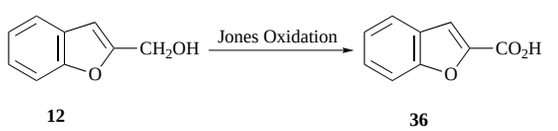
24 **33**

Scheme 4



27,29 **34,35**

27, 34 Ar = Ph
29, 35 Ar = C_6H_4OMe-*p*



12 **36**

Scheme 5

Thus, we have described an excellent method for the synthesis of benzofurans by palladium-catalysed heteroannulation of *o*-iodophenol with acetylenic substrates. Although a similar method was reported[42] earlier, our method differs significantly in the use of bis(triphenylphosphine)palladium(II) chloride–cuprous iodide as the catalytic system and triethylamine as a base using dimethylformamide as the solvent. Earlier workers[42] have used bis(triphenylphosphine)palladium(II) acetate–cuprous iodide in piperidine. However, our experience with use of palladium(II) acetate with or without triphenylphosphine showed that only poor yields of benzofurans were obtained. Also, significantly, it has been possible for us to isolate the acyclic product **30** from the palladium-catalysed reaction in the presence of a PTC (entries 6 and 7, Table 1) which we have shown to be an intermediate in the formation of the benzofurans. Thus, a complete mechanism of the reaction has been established. The transformation of some of the benzofurans to biologically active compounds has also been accomplished.

Experimental

Mps were determined in an open sulfuric acid bath and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrometer in spectrophotometric grade ethanol (Baker). IR spectra were taken on a Perkin-Elmer 298 instrument as KBr plates (solid) or neat (liquid). ^{1}H NMR spectra were recorded on a Varian EM-360, a Varian XL-200 and a Bruker DPX-300 spectrometer in solvents as indicated with tetramethylsilane as internal reference; *J* values given in Hz. Silica gel TLC was performed on 60F-254 pre-coated sheets (E. Merck) and column chromatography was done on silica gel (60–120 mesh) or neutral alumina. Elemental analyses were performed on a Perkin-Elmer 240C analyser. Aryl acetylenes[61] **10**, **11** and acetylenic carbinols[62] **13**–**18** were synthesised according to a literature procedure. Prop-2-ynyl alcohol **12** was bought from the Aldrich Chemical Company, UK.

General method for the synthesis of 2-substituted benzo[*b*]furans 21–29

To a well-stirred mixture of *o*-iodophenol **9** (2 mmol), Pd-$(Ph_3P)_2Cl_2$ (2–3.5 mol%), CuI (3–5 mol%) and triethylamine (2 equiv.) in DMF (5 ml) an acetylenic compound, **10**–**18**, was added under an N_2 atmosphere. The mixture was stirred at room temperature for a further period of 1 h and then according to the conditions indicated in Table 1. The mixture was then cooled, poured into water (100 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were washed with 5 mol dm^{-3} aq. NaOH (3 × 100 ml) and water (3 × 100 ml), dried (Na_2SO_4) and evaporated. The residue on column chromatography afforded the 2-substituted benzofurans.

2-Phenylbenzofuran 21. Yield 77%; mp 118–120 °C (lit.,[63] 120.8–121.2 °C); λ_{max}(EtOH)/nm 316 (log ε 4.15), 308.3 (4.29), 261.4 (3.88) and 226 (3.99); δ_H(200 MHz, $CDCl_3$) 7.06 (s, 1H, 3-H), 7.23–7.65 (m, 8H, ArH) and 7.88–7.96 (m, 1H, ArH); δ_C(75 MHz, $CDCl_3$) 101.241, 111.123, 120.848, 121.715, 122.874, 124.202, 124.865, 128.395, 128.496, 128.735, 129.151, 129.167, 130.406 and 132.452.

2-(*m*-Chlorophenyl)benzofuran 22. Yield 61%; mp 88–90 °C; ν_{max}(KBr)/cm^{-1} 1600, 1500, 1470 and 1450; λ_{max}(EtOH)/nm 319.2 (log ε 4.33), 304 (4.44) and 232.4 (4.10); δ_H(300 MHz, $CDCl_3$) 7.10 (s, 1H, 3-H), 7.20–7.40 (m, 4H, ArH), 7.45–7.60 (m, 2H, ArH), 7.70 (m, 1H, ArH) and 7.85 (s, 1H, ArH) (Found: C, 73.21; H, 4.06. $C_{14}H_9ClO$ requires C, 73.53; H, 3.96%).

2-Hydroxymethylbenzofuran 23.[64] Yield 68%; bp 52–53 °C/0.03 mmHg; ν_{max}(KBr)/cm^{-1} 3340, 1450 and 1255; λ_{max}(EtOH)/nm 283.3 (log ε 3.52), 277 (3.50), 247.4 (4.10) and 210 (4.20); δ_H(200 MHz, $CDCl_3$) 2.16 (s, 1H, OH), 4.76 (s, 2H, CH_2), 6.68 (s, 1H, 3-H), 7.20–7.36 (m, 2H, ArH) and 7.48–7.60 (m, 2H, ArH) (Found: C, 72.58; H, 5.59. $C_9H_8O_2$ requires C, 72.95; H, 5.44%).

2-(2′-Hydroxyisopropyl)benzofuran 24.[58a] Yield 75%; bp 68 °C/0.005 mmHg; ν_{max}(KBr)/cm^{-1} 3380, 2980 and 1450; λ_{max}(EtOH)/nm 283.3 (log ε 3.52), 275.9 (3.50), 247 (4.12) and 208.8 (4.27); δ_H(200 MHz, $CDCl_3$) 1.66 (s, 6H, 2 × CH_3), 2.20 (s, 1H, OH), 6.60 (s, 1H, 3-H), 7.20–7.32 (m, 2H, ArH) and 7.46–7.58 (m, 2H, ArH) (Found: C, 74.84; H, 7.21. $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%).

3-(*o*-Hydroxyphenyl)-1,1-dimethylprop-2-yn-1-ol 30. Mp 85–86 °C; ν_{max}(KBr)/cm^{-1} 3380, 2220 and 1600; λ_{max}(EtOH)/nm 295.6 (log ε 3.65), 251.2 (4.07), 240.4 (4.03) and 211.2 (4.39); δ_H(200 MHz, $CDCl_3$) 1.66 (s, 6H, 2 × CH_3), 6.48–7.01 (m, 2H, ArH) and 7.22–7.36 (m, 2H, ArH) (Found: C, 74.88; H, 6.67. $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%).

2-(Tetrahydropyranyloxymethyl)benzofuran 25. Yield 54.7%; viscous liquid; ν_{max}(KBr)/cm^{-1} 2960, 2880, 1460 and 1360; λ_{max}(EtOH)/nm 247.6 (log ε 4.17), 277.0 (3.52) and 284.0 (3.50); δ_H(60 MHz, CCl_4) 1.46–1.83 (m, 6H, 3′-, 4′-, 5′-H), 3.50–4.03 (m, 3H, 2′, 6′-H), 4.63 (s, 2H, CH_2), 6.63 (s, 1H, 3-H) and 7.13–7.66 (m, 4H, ArH) (Found: C, 72.43; H, 7.04. $C_{14}H_{16}O_3$ requires C, 72.38; H, 6.94%).

2-(1′-Hydroxybut-2′-enyl)benzofuran 26. Yield 88%; bp 78–80 °C/0.002 mmHg; ν_{max}(KBr)/cm^{-1} 3345, 1600 and 1585; λ_{max}(EtOH)/nm 284.0 (log ε 3.69), 277.4 (3.67), 249.2 (4.18) and 209.8 (4.29); δ_H(200 MHz, $CDCl_3$) 1.81 (d, *J* 4, 3H, CH_3), 5.34 [d, *J* 5, 1H, C*H*(OH)], 5.90–5.94 (m, 2H, CH=CH), 6.68 (s, 1H, 3-H), 7.24–7.36 (m, 2H, ArH) and 7.52–7.62 (m, 2H, ArH) (Found: C, 76.64; H, 6.71. $C_{12}H_{12}O_2$ requires C, 76.56; H, 6.42%).

Benzofuran-2-yl(phenyl)methanol 27. Yield 67%; mp 73–74 °C; ν_{max}(KBr)/cm^{-1} 3200, 1595, 1585, 1490 and 1450; λ_{max}(EtOH)/nm 284.4 (log ε 3.71), 277.5 (3.72) and 249.5 (4.28); δ_H(300 MHz, $CDCl_3$) 2.54 (br s, 1H, OH), 5.95 (s, 1H, C*H*OH),

6.52 (s, 1H, 3-H) and 7.19–7.55 (m, 9H, ArH); δ_C(75 MHz, $CDCl_3$) 70.611 (CHOH), 103.999 (C-3), 111.280, 121.089, 122.779, 124.260, 126.740, 127.935, 128.343, 128.565, 140.180, 155.022 and 158.403 (ArC); δ_C(75 MHz, $CDCl_3$, DEPT 135) 70.795 (CHOH) 104.189 (C-3), 111.468, 121.277, 122.966, 124.446, 126.929, 128.533 and 128.754 (ArC) (Found: C, 80.71; H, 5.24. $C_{15}H_{12}O_2$ requires C, 80.34; H, 5.39%).

***o*-Methylphenyl(benzofuran-2-yl)methanol 28.** Yield 72%; mp 72 °C; ν_{max}(KBr)/cm^{-1} 3360, 3310, 1610, 1600, 1580, 1490, 1470 and 1450; λ_{max}(EtOH)/nm 284.8 (log ε 3.66), 277.8 (3.67) and 250.2 (4.21); δ_H(300 MHz, $CDCl_3$) 2.36 (s, 3H, $ArCH_3$), 6.14 (s, 1H, C*H*OH), 6.41 (s, 1H, 3-H), 7.20–7.29 (m, 5H, ArH) and 7.45–7.56 (m, 3H, ArH); δ_C(75 MHz, $CDCl_3$) 19.032 (CH_3), 67.502 (CHOH), 104.223 (C-3), 111.295, 121.081, 122.762, 124.253, 126.285, 126.344, 127.979, 128.171, 130.496, 135.531, 138.221, 155.044 and 158.108 (Found: C, 80.28; H, 5.48. $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92%).

***p*-Methoxyphenyl(benzofuran-2-yl)methanol 29.** Yield 64%; mp 75–76 °C; ν_{max}(KBr)/cm^{-1} 2920, 2840, 1490 and 1450; λ_{max}(EtOH)/nm 284.8 (log ε 3.76), 277.6 (3.81) and 251.2 (4.23); δ_H(60 MHz, $CDCl_3$) 3.33 (br s, 1H, CHO*H*), 3.73 (s, 3H, $ArOCH_3$), 5.78 (s, 1H, C*H*OH), 6.46 (s, 1H, 3-H) and 6.73–7.57 (m, 8H, ArH) (Found: C, 75.28; H, 5.42. $C_{16}H_{14}O_3$ requires C, 75.57; H, 5.55%).

2-Isopropenylbenzofuran 33.[58] To a solution of compound **24** (110 mg, 0.62 mmol) in pyridine (10 ml) under anhydrous conditions was added $POCl_3$ (287 mg, 1.87 mmol). The mixture was stirred at room temperature for 48 h and then poured into ice–cold water (100 ml) and extracted with ether (3 × 50 ml). The combined extracts were washed with dilute hydrochloric acid, dried (Na_2SO_4) and evaporated. The residue upon vacuum distillation afforded the title compound **33** (83%), ν_{max}(KBr)/cm^{-1} 1610, 1550 and 1450; λ_{max}(EtOH)/nm 301.8 (log ε 3.87), 294.2 (3.93), 283.5 (3.98) and 206.0 (4.03); δ_H(200 MHz, $CDCl_3$) 2.12 (d, *J* 1, 3H, CH_3), 5.20–5.22 (m, 1H, H_2C=C), 5.84 (d, *J* 1, 1H, H_2C=C), 6.68 (s, 1H, 3-H), 7.20–7.36 (m, 2H, ArH) and 7.46–7.60 (m, 2H, ArH).

General method for the synthesis of 2-aroylbenzofurans 34 and 35. To a solution of aryl(benzofuran-2-yl)methanol (0.89 mmol) in dry dichloromethane (10 ml) was added finely powdered active manganese dioxide (1.20 g, 13.80 mmol). The mixture was stirred at room temperature for 24 h after which it was passed through a bed of Celite, the residue being washed with dichloromethane (3 × 25 ml). The filtrate was evaporated and the residue upon column chromatography and/or crystallisation afforded the 2-aroylbenzofuran.

2-Benzoylbenzofuran 34. Yield 91%; mp 89 °C (lit.,[59] 90 °C); ν_{max}(KBr)/cm^{-1} 1645, 1610, 1600 and 1550; λ_{max}(EtOH)/nm 312.2 and 227.7; δ_H(300 MHz, $CDCl_3$) 7.33–7.74 (m, 8H, ArH), 8.02–8.05 (m, 2H, ArH); δ_C(75 MHz, $CDCl_3$) 112.525 (C-3), 116.589, 123.277, 123.941, 126.934, 128.359, 128.500, 129.390, 132.872, 137.161, 152.106, 155.942 and 184.415 (CO); δ_C(75 MHz, $CDCl_3$ DEPT 135) 112.712, 116.792, 123.469, 124.131, 128.553, 128.690, 129.576 and 133.063.

2-(*p*-Methoxybenzoyl)benzofuran 35. Yield 86.4%; mp 95–96 °C (lit.,[59] 97 °C); ν_{max}(KBr)/cm^{-1} 1630, 1605, 1580 and 1550; λ_{max}(EtOH)/nm 322.2 and 282.2; δ_H(300 MHz, $CDCl_3$) 3.89 (s, 3H, $ArOCH_3$), 6.99–7.02 (m, 2H, ArH), 7.31–7.70 (m, 5H, ArH) and 8.08–8.11 (m, 2H, ArH); δ_C(75 MHz, $CDCl_3$) 55.964 (OCH_3), 112.904, 114.256, 115.983, 123.571, 124.295, 127.457, 128.441, 130.226, 132.385, 153.057, 156.218, 164.009 and 183.304 (CO).

Synthesis of benzofuran-2-carboxylic acid 36

To a pre-cooled (ice-bath) solution of compound **12** in acetone, Jones reagent (CrO_3, H_2SO_4 in water) was added until the colour of the reagent persisted. The excess reagent was decomposed with isopropyl alcohol and then extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was crystallised from methanol to give compound **36**; overall yield from compound **12** was 75%; mp 194–196 °C (lit.,[60] 195–198 °C); ν_{max}(KBr)/cm^{-1} 1700, 1590, 1440 and 1310; λ_{max}(EtOH)/nm 265.8 (log ε 3.13) and 293.4 (2.67); δ_H(60 MHz, $CDCl_3$) 7.26–7.83 (m, ArH).

Conversion of 3-(*o*-hydroxyphenyl)-1,1-dimethylprop-2-yn-1-ol 30 into 2-(2′-hydroxyisopropyl)benzofuran 24

A solution of the acyclic compound **30** (100 mg, 0.57 mmol) in Et_3N was heated under an N_2 atmosphere at 60 °C for 6 h after which it was evaporated. The residue was treated with water (25 ml) and then extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were washed with 5 mol dm^{-1} aqueous NaOH (3 × 50 ml) and water (3 × 50 ml), dried (Na_2SO_4) and evaporated. The residue upon column chromatography afforded a colourless liquid which was found to be identical with 2-(2′-hydroxyisopropyl)benzofuran **24**, obtained by the one-step procedure as described above, from comparison of IR, UV and ^{1}H NMR spectra.

Synthesis of 3-(*o*-acetoxyphenyl)-1-phenylprop-2-yn-1-ol 32

To a well-stirred mixture of *o*-acetoxyiodobenzene **31** (1.91 mmol), $Pd(Ph_3P)_2Cl_2$ (45 mg, 0.064 mmol) and CuI (20 mg, 0.105 mmol) in Et_3N (a few drops of DMF was used to facilitate dissolution) was added 1-phenylprop-2-yn-1-ol (380 mg, 2.87 mmol) under an N_2 atmosphere. The mixture was further stirred at room temperature for 24 h after which it was evaporated under reduced pressure. The residue was treated with water (50 ml) and extracted with $CHCl_3$ (3 × 50 ml). The combined extracts were washed with water (3 × 50 ml), dried (Na_2SO_4) and evaporated. The resulting residue on column chromatography (silica gel 60–120 mesh) with 10% $CHCl_3$ in light petroleum (bp 60–80 °C) afforded the title compound **32** as a light yellow oil (86.4%); ν_{max}(KBr)/cm^{-1} 3440br, 2220, 1770, 1490 and 1450; λ_{max}(EtOH)/nm 285.4 (log ε 3.47), 277.6 (3.466), 243.2 (4.26) and 253.0 (4.31); δ_H(60 MHz, CCl_4) 2.0 (s, 3H, CH_3), 4.13 (s, 1H, OH), 5.53 (s, 1H, C*H*OH) and 6.90–7.66 (m, 9H, ArH) (Found: C, 76.38; H, 5.37. $C_{17}H_{14}O_3$ requires C, 76.67; H, 5.30%).

Cyclisation of 3-(*o*-acetoxyphenyl)-1-phenylprop-2-yn-1-ol 32 into benzofuran-2-yl(phenyl)methanol 27

Sodium (10 mg, 0.37) was dissolved in dry ethanol (5 ml) under an N_2 atmosphere. To this solution was added 3-(*o*-acetoxyphenyl)-1-phenylprop-2-yn-1-ol **32** in dry ethanol (5 ml). The mixture was refluxed for 2 h after which it was evaporated under reduced pressure. The residue was treated with water (25 ml), acidified (pH 5–6) with 6 M aqueous HCl and extracted with $CHCl_3$ (3 × 75 ml). The combined extracts were washed with water (3 × 75 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was column chromatographed with $CHCl_3$–light petroleum (1:1) as eluent to give a light yellow solid which was found to be identical with benzofuran-2-yl(phenyl)methanol **27** (mp, IR, UV and ^{1}H NMR).

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