A Versatile Two-Stage Synthesis of 2-Substituted Benzo[*b*]furans from (2-Methoxyphenyl)ethynes

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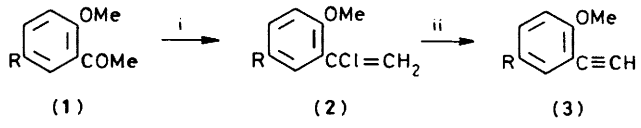
(2-Methoxyphenyl)ethynes react with aryl or alkyl halides to give disubstituted alkynes which are converted into the corresponding 2-substituted benzo[*b*]furans on treatment with lithium iodide in 2,4,6-trimethylpyridine.

The synthesis of 2-substituted benzo[*b*]furans usually involves the cyclization of appropriate *ortho*-disubstituted benzenes,[1] although a number of alternative procedures, such as lithiation of the preformed parent benzofuran and subsequent attack by a suitable electrophile, are known.[2] These methods, however, are frequently limited in their versatility by the availability of requisite precursors. During work directed towards the synthesis of 2-alkynylphenols we have found a simple and highly versatile route to benzo[*b*]furans, from readily available acetophenones, *via* derivatives of (2-methoxyphenyl)ethyne. Thus, chlorination of a suitable 2-methoxyacetophenone (**1**) (Scheme 1) and subsequent dehydrohalogenation of the intermediate chloroalkene (**2**) results in moderate yields (51—72% overall) of the corresponding alkynes (**3**),[3] which undergo facile alkylation with alkyl iodides to give (**4**) (Scheme 2, Table 1). Arylated derivatives, such as (**4h**), are conveniently prepared from (**3**) and an appropriate aryl halide under the palladium catalysed Heck conditions.[4]

Reaction of (**4**) with lithium iodide in 2,4,6-trimethylpyridine at reflux [5] gave not the expected phenols, but resulted instead in smooth formation of the corresponding 2-substituted benzo[*b*]-furans (**5**) in moderate to good yields (Table 2). A similar



a; R = H; b; R = Me; c; R = OMe

Scheme 1. *Reagents:* i, PCl_5; ii, KOH; EtOH, Heat.

a; R = H, R′ = Me
b; R = H, R′ = Et
c; R = H, R′ = Pr^i
d; R = H, R′ = n-C_6H_{13}
e; R = Me, R′ = n-C_6H_{13}
f; R = OMe, R′ = n-C_6H_{13}
g; R = OH, R′ = n-C_6H_{13}
h; R = H, R′ = Ph

Scheme 2. *Reagents:* LiI, 2,4,6-trimethylpyridine, heat.

Table 1. Physical and analytical data for 1-(2-methoxyphenyl)alkynes

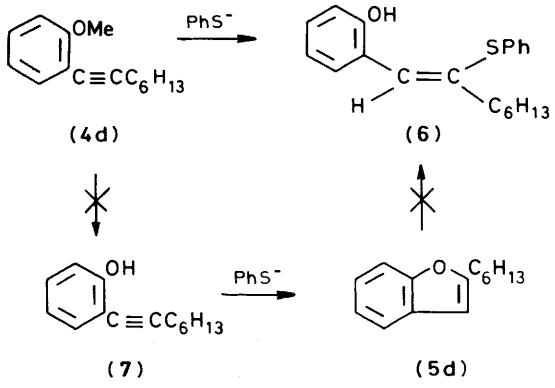
Compd.	B.p. (°C) (Torr)	Yield (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
(**4a**)	150 (0.5)	72	$C_{10}H_{10}O{\cdot}0.25H_2O$	79.6	7.05	79.7	7.0
(**4b**)	Oil	95	$C_{11}H_{12}O$	82.25	7.55	82.45	7.55
(**4c**)	150 (0.1)	38	$C_{12}H_{14}O$	82.75	8.2	82.7	8.1
(**4d**)	Oil	86	$C_{15}H_{20}O{\cdot}0.25H_2O$	81.75	9.05	81.6	9.35
(**4e**)	Oil	98	$C_{16}H_{22}O$	83.15	9.65	83.45	9.65
(**4f**)	190 (0.2)	86	$C_{16}H_{22}O_2{\cdot}0.25H_2O$	76.7	8.95	76.6	9.05

Table 2. Physical and analytical data for 2-substituted benzofurans

Compd.	B.p. (°C) (Torr)	Lit. b.p. °C (Torr)	Yield (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
(**5a**)	50 (0.2)	197—198 [16]	61	C_9H_8O				
(**5b**)	108 (15)	100—102 [17] (15)	90	$C_{10}H_{10}O$				
(**5c**)	40—45 (0.1)	110—116 [18] (20)	72	$C_{11}H_{12}O$	82.6	7.95	82.45	7.55
(**5d**)	Oil		58	$C_{14}H_{18}O{\cdot}0.25H_2O$	81.3	8.6	81.3	9.0
(**5e**)	Oil		92	$C_{15}H_{20}O$	82.9	9.3	83.25	9.3
(**5f**)	Oil		56	$C_{15}H_{20}O_2$	77.6	8.85	77.55	8.7
(**5g**)	M.p. 48—49 (hexane)		20	$C_{14}H_{18}O_2$	77.45	8.4	77.05	8.3
(**5h**)	M.p. 119—120	121 [19]	91	$C_{14}H_{10}O$	86.7	5.15	86.6	5.2

observation with pyridine hydrochloride has previously been reported to give 2-arylbenzofurans,[6] but has not been validated for alkylated analogues. Presumably initial dealkylation occurs under the reaction conditions followed by a subsequent 5-*endo-dig* attack of the resulting phenoxide on the triple bond. Such cyclizations are favoured reactions [7] and are in accord with the known ability of 2-alkynylphenols to cyclize under alkaline conditions.[8,9] The generality of the reaction is illustrated by the examples of Scheme 2. Of particular note is the ability to obtain reasonable yields of the methoxybenzofuran (**5f**) accompanied by only relatively small quantities of the demethylation product (**5g**).

Attempts to effect dealkylation with other reagents, either with or without concomitant cyclization, were generally unsuccessful. Thus, thiolate anion, generated *in situ* from ethanethiol and sodium hydride in *N*,*N*-dimethylformamide,[10] resulted in the gradual decomposition of the alkyne (**4d**), while thiophenoxide,[11] although resulting in extensive decomposition, afforded the alkyne addition product (**6**) (Scheme 3) as the only

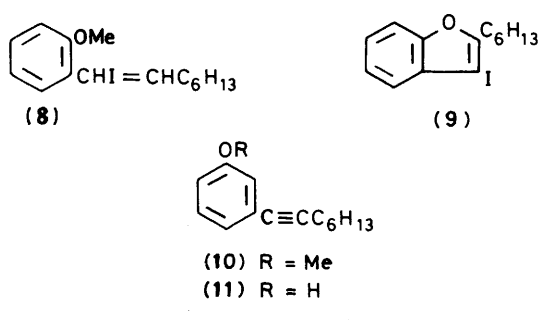


Scheme 3.

isolable product. That (**6**) was derived directly from (**4d**), and not *via* the phenol (**7**) or the benzofuran (**5d**), was demonstrated by treating both (**7**) and (**5d**) with thiophenoxide anion under similar reaction conditions. In neither of these instances was the formation of (**6**) detected, although the expected transformation of (**7**) into the benzofuran (**5d**) proceeded almost quantitatively.

Attempts to dealkylate (**4d**) with iodotrimethylsilane [12] gave only the unstable hydrogen iodide addition product (**8**). The assigned regiochemistry of (**8**) is in accord with ^{1}H n.m.r. spectral data, and with studies on hydrogen chloride addition to 1-arylalkynes,[13] but the stereochemistry is not known.

That the above cyclizations are dependent on a proton source was demonstrated by the treatment of (**7**) with n-butyl-lithium in tetrahydrofuran, when no reaction occurred even after 24 h at reflux. Addition of excess of ethanol, however, allowed the cyclization to proceed. In an interesting extension to the reaction, it was found that the addition of iodine (1 equiv.) to a solution of the anion of (**7**) in tetrahydrofuran resulted in the



trapping of the intermediate anion as the iodo derivative (**9**). This suggests that other 3-substituted 2-alkyl or aryl benzofurans might be similarly prepared. As expected, the (3-methoxyphenyl)alkyne (**10**), which was prepared in a similar manner to that of the 2-methoxylated derivatives, formed the phenol (**11**) almost quantitatively on treatment with lithium iodide in 2,4,6-trimethylpyridine at reflux.

Experimental

M.p.s were determined using a Büchi apparatus. I.r. spectra were measured as liquid films (for oils) or for dispersions in Nujol (for solids) using a Perkin-Elmer 197 spectrophotometer. N.m.r. spectra were obtained with a Varian EM 390 (90 MHz) spectrometer for solutions in deuteriochloroform with $SiMe_4$ as the standard. Mass spectral data was obtained from a VG-Micromass 70-70F instrument using electron impact or ammonia chemical ionization techniques as indicated. The yields for all products are for chromatographically homogeneous material, and the recorded b.p.s are those obtained by Kugelrohr distillation.

2-*Methoxy*-5-*methylacetophenone* (**1b**).—Methyl iodide (5.02 ml, 80 mmol) was added to a stirred mixture of 2-hydroxy-5-methylacetophenone (10.0 g, 67 mmol) and anhydrous potassium carbonate (9.19 g, 67 mmol) in dry *N*,*N*-dimethylformamide (120 ml) and the mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed with chloroform on silica gel to give the ether (**1b**) (71.6 g, 65%) as a colourless oil (Found: C, 72.85; H, 7.2. Calc. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.35%).

(2-*Methoxy*-5-*methylphenyl*)*ethyne* (**3b**).—A solution of (**1b**) (6.11 g, 37 mmol) in dry benzene (5 ml) was added dropwise with stirring to phosphorus pentachloride (7.95 g, 37 mmol) in dry benzene (15 ml) and the initial exotherm was allowed to subside. The mixture was then heated to reflux for 5 h to complete the reaction before cooling and addition to water. The organic material was extracted into ether and the extracts were thoroughly washed with water and dried ($MgSO_4$). Evaporation and chromatography with dichloromethane–hexane (1:4) on silica gel then gave essentially pure 1-chloro-1-(2-methoxy-5-methylphenyl)ethene (**2b**) (5.08 g, 75%) which was used without further purification. To this material (5.0 g) was added a solution of potassium hydroxide (4.59 g) in ethanol (50 ml) and the resulting solution was refluxed for 48 h and then cooled. After dilution with water, the product was extracted into ether and the dried extracts were evaporated to a yellow oil. Chromatography on silica gel eluting with dichloromethane–hexane (1:1) then afforded the *alkyne* (**3b**) (2.18 g, 55%) as a colourless oil; $\nu_{max.}$ 3 280, 2 100, 1 610, 1 585, 1 505, 1 465, and 1 445 cm^{-1}; δ 2.23 (3 H, s, ArMe), 3.22 (1 H, s, methine), 3.84 (3 H, s, OMe), 6.75 (1 H, d, *J* 9 Hz, 3-H), 7.10 (1 H, dd, *J* 2, 9 Hz, 4-H), and 7.24 (1 H, d, *J* 2.5 Hz, 6-H) (Found: C, 82.35; H, 7.15. $C_{10}H_{10}O$ requires C, 82.15; H, 6.9%).

(2,5-*Dimethoxyphenyl*)*ethyne* (**3c**).—Using the same procedure as described above, 2,5-dimethoxyacetophenone (12.5 g, 70 mmol) was converted into essentially pure chloroethene (**2c**) (11.18 g, 80%). Dehydrohalogenation of this material (10.0 g) then gave the *ethyne* (**3c**) (6.57 g, 81%); m.p. (hexane–ether) 39—40 °C; $\nu_{max.}$ 3 280, 3 250, 2 100, 1 605, and 1 585 cm^{-1}; δ 3.26 (1 H, s, methine), 3.75 (3 H, s, OMe), 3.84 (3 H, s, OMe), 6.85 (2 H, m, 2-H, 4-H), 7.00 (1 H, m, 6-H) (Found: C, 74.05; H, 6.2. $C_{10}H_{10}O_2$ requires C, 73.8; H, 6.3%).

General Procedure for the Alkylation of (**3a**—**c**).—To a stirred solution of (**3**) (20 mmol) in dry tetrahydrofuran (50 ml) at

−70 °C under nitrogen was added 1.55M n-butyl-lithium in hexane (1.3 ml, 20 mmol) and the mixture was stirred for 30 min at room temperature. After re-cooling to −70 °C, the alkyl iodide (20 mmol) was added dropwise with stirring and the reaction mixture was allowed to warm to room temperature before heating to reflux for 18 h. Dilute hydrochloric acid was added to the cooled mixture and the product was extracted with ether, dried ($MgSO_4$), evaporated, and chromatographed to yield pure (**4a**—**f**) (Table 1).

1-(2-*Methoxyphenyl*)-2-*phenylethyne* (**4h**).—Palladium(II) acetate (85 mg, 0.379 mmol) was added to a stirred, deaerated solution of phenyl iodide (1.54 g, 57 mmol), triphenylphosphine (199 mg, 0.757 mmol), and (**3a**) (1.00 g, 7.57 mmol) in dry triethylamine (30 ml) and the mixture was heated to 80 °C under a nitrogen atmosphere for 4 h. After cooling, the mixture was poured into dilute hydrochloric acid and the product was extracted into ether. Evaporation of the dried extracts and chromatography with dichloromethane–hexane (1:4) on silica gel afforded pure (**4h**) (0.84 g, 53%) as a colourless oil; b.p. 150 °C (0.2 Torr) [lit.,[9b] b.p. 144—145 °C (0.2 Torr)].

General Procedure for Benzofuran Synthesis.—Lithium iodide (1.34 g, 10 mmol) was added to a solution of the alkyne (**4**) (5 mmol) in dry 2,4,6-trimethylpyridine (30 ml) and the mixture was stirred at reflux under nitrogen for 18—30 h. After cooling, the dark reaction mixture was poured into dilute hydrochloric acid and the product was extracted into ether, and the extract washed with water, dried, and evaporated. Chromatography then afforded the pure benzofurans indicated in Table 2. In the case of the dimethoxyalkyne (**4f**) some 20% yield of the phenol (**5g**) was also isolated.

Attempted Demethylation of (**4d**).—(*a*) *With thiophenoxide.*[11] Sodium hydride (0.92 g, 23 mmol of a 60% dispersion in mineral oil) was added under nitrogen to a stirred solution of thiophenol (2.35 ml, 23 mmol) in ethane-1,2-diol (25 ml) and the reaction was stirred for 0.5 h to complete the formation of the sodium salt. A solution of (**4d**) (0.50 g, 2.3 mmol) in ethane-1,2-diol (2 ml) was then added and the mixture was heated to reflux for 18 h. After cooling, an excess of 2M-sulphuric acid was added and the organic material was extracted into ether. Evaporation of the dried ethereal phase and chromatography with dichloromethane–hexane (1:1) on silica gel then gave (Z)-1-(2-*hydroxyphenyl*)-2-*phenylthio-oct*-1-*ene* (**6**) (100 mg, 14%) as a crystalline solid; $\nu_{max.}$ 3 400, 1 603, and 1 585 cm^{-1}; δ 0.86 (3 H, distorted t, Me), 1.24 (6 H, m, alkylene envelope), 1.56 (2 H, m, homoallylic CH_2), 2.30 (2 H, t, *J* 7.5 Hz, allylic CH_2), 5.37 (1 H, exchangeable s, OH), 6.88 (1 H, d, *J* 0.8 Hz, vinylic CH), 7.26 (2 H, m, 3-H, 5-H), and 7.25 (7 H, m, ArH); *m/z* 312 (M^+, 40%) 284 (8), 227 (6), 203 (100), 175 (15), 133 (45), 132 (30), 131 (53), 119 (33), 107 (47), 91 (68), and 77 (22); M^+, 312.1543 ($C_{20}H_{24}OS$ requires 312.1548) (Found: C, 76.6; H, 7.6; S, 10.2. $C_{20}H_{24}OS$·0.25H_2O requires C, 76.4; H, 7.25; S, 10.2%).

(*b*) *With Iodotrimethylsilane.*[12].—Sodium iodide (90 mg, 0.6 mmol) was added to a stirred solution of (**4d**) (100 mg, 0.46 mmol) in dry acetonitrile (5 ml) under nitrogen. Chlorotrimethylsilane (65.2 mg, 0.6 mmol) was then added, whereby an immediate precipitate of sodium chloride was formed. The resulting mixture was stirred at 60 °C overnight and the cooled solution was diluted with water. Extraction of the product into ether followed by thorough washing of the extract with sodium thiosulphate gave a colourless solution, which after drying and evaporation afforded the iodo compound (**8**) (100 mg, 63%) as an unstable, colourless oil; $\nu_{max.}$ 2 950, 2 920, 2 850, 1 595, and 1 575 cm^{-1}; δ 0.82 (3 H, distorted t, Me), 1.28 (6 H, m, alkylene envelope), 1.80 (2 H, m, allylic CH_2), 3.82 (3 H, s, OMe), 6.48 (1 H, t, *J* 7.5 Hz, vinylic CH), and 7.02 (4 H, complex m, ArH); *m/z* (NH_3 c.i.) 344 (M^+).

1-(2-*Hydroxyphenyl*)*oct*-1-*yne* (**7**).—To a stirred suspension of lithium amide [from lithium (0.59 g, 85 mmol)] in liquid ammonia (250 ml) was added (2-hydroxyphenyl)ethyne[14] (5.0 g, 42 mmol) in dry tetrahydrofuran (80 ml) and the mixture was stirred at *ca.* −30 °C for 1 h. Hexyl iodide (6.13 ml, 42 mmol) in tetrahydrofuran (80 ml) was added, and the mixture allowed to reflux for 6 h before evaporation of the ammonia overnight. The resulting brown solution was refluxed for 18 h, cooled, and poured into dilute aqueous sulphuric acid. The product was extracted into ether and the extract then evaporated and the residue distilled to give the *product* (**7**) (6.76 g, 80%) as a colourless oil, b.p. 120—140 °C (0.1 Torr); $\nu_{max.}$ 3 500, 1 608, 1 575, 1 485, and 1 463 cm^{-1}; δ 0.89 (3 H, distorted t, Me), 1.40 (8 H, m, alkylene envelope), 2.43 (2 H, t, *J* 7 Hz, C≡CCH_2), 5.80 (1 H, exchangeable s, OH), 6.87 (2 H, m, ArH), and 7.22 (2 H, m, ArH) (Found: C, 79.65; H, 8.8. $C_{14}H_{18}O$·0.5H_2O requires C, 79.6; H, 9.05%).

Cyclization of (**7**) *with Thiophenoxide.*—Reaction of (**7**) (0.50 g, 2.5 mmol) with thiophenoxide anion [from thiophenol (2.53 ml, 25 mmol)], as described above for the attempted demethylation of (**4d**), afforded after chromatography the benzofuran (**5d**) (0.47 g, 94%), which was spectroscopically identical with the material prepared using the general procedure above.

2-*Hexyl*-3-*iodobenzo*[b]*furan* (**9**).—To a solution of (**7**) (0.33 g, 1.63 mmol) in dry tetrahydrofuran (8 ml) at −70 °C under nitrogen was added 1.55M-n-butyl-lithium in hexane (1.06 ml, 1 equiv.) and the mixture was warmed to room temperature. Iodine (0.418 g, 1 equiv.) was added to the red solution and the mixture was heated at reflux overnight. After cooling, the mixture was diluted with water and the product was extracted into ether. The ethereal solution was washed with aqueous sodium thiosulphate and water and then dried. Evaporation afforded a pale yellow oil which after chromatography with dichloromethane–hexane (1:4) gave (**9**) (227 mg, 42%) as an oil; $\nu_{max.}$ 2 960, 2 930, 2 860, 1 585, 1 450, and 1 255 cm^{-1}; δ 0.91 (3 H, distorted t, Me), 1.36 (6 H, m, alkylene envelope), 1.80 (2 H, m, homoallylic CH_2), 2.82 (2 H, t, *J* 6 Hz, allylic CH_2), and 7.26 (4 H, br m, ArH); *m/z* 328 (M^+, 47%), 257 (100), 131 (55), and 102 (18) (Found: M^+, 328.0329. $C_{14}H_{17}IO$ requires 328.0325).

1-(3-*Methoxyphenyl*)*oct*-1-*yne* (**10**).—Alkylation of (3-methoxyphenyl)ethyne[15] (5.0 g, 38 mmol) with hexyl iodide (8.0 g, 38 mmol), ad described above under the general alkylation procedure, gave the *alkyne* (**10**) (6.98 g, 85%) as a colourless oil, b.p. 50—60 °C (0.2 Torr); $\nu_{max.}$ 2 225, 1 605, 1 600, 1 585, 1 575, 1 490, 1 480, and 1 465 cm^{-1}; δ 0.88 (3 H, distorted t, Me), 1.37 (8 H, m, alkylene envelope), 2.36 (2 H, t, *J* 6 Hz, C≡CCH_2), 3.74 (3 H, s, OMe), 6.92 (3 H, m, ArH), and 7.16 (1 H, t, *J* 7 Hz, ArH) (Found: C, 83.1; H, 9.4. $C_{15}H_{20}O$ requires C, 83.3; H, 9.3%).

1-(3-*Hydroxyphenyl*)*oct*-1-*yne* (**11**).—Reaction of (**10**) (6.50 g, 30 mmol) with lithium iodide in 2,4,6-trimethylpyridine as described above gave, after chromatography, the phenol (**11**) (5.40 g, 90%) as a colourless oil; $\nu_{max.}$ 3 400, 2 230, 1 605, 1 590, and 1 580 cm^{-1}; δ 0.85 (3 H, distorted t, Me), 1.39 (8 H, m, alkylene envelope), 2.32 (2 H, t, *J* 6 Hz, C≡CCH_2), 4.47 (1 H, exchangeable s, OH), 6.78 (2 H, m, ArH), and 7.02 (2 H, m, ArH) (Found: C, 83.0; H, 9.15. $C_{14}H_{18}O$ requires C, 83.1; H, 8.95%).

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