Palladium-catalysed heteroannulation with terminal alkynes: synthesis of phthalides[1]

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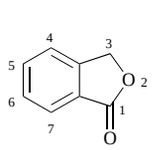
The palladium–copper-catalysed heteroannulation of *o*-iodobenzoic acid 3 with terminal alkynes 4–18 leads to the synthesis of (*Z*)-3-alkylidenephthalides 19–33 as the major products. In certain cases, the formation of isocoumarins 34–37 is also observed.

Compounds containing the phthalide [isobenzofuran-1(3*H*)-one] **1** structure have drawn considerable interest. For example, the occurrence of 3-alkylidenephthalides **2** in umbelliferous



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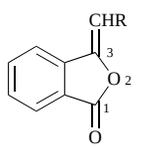


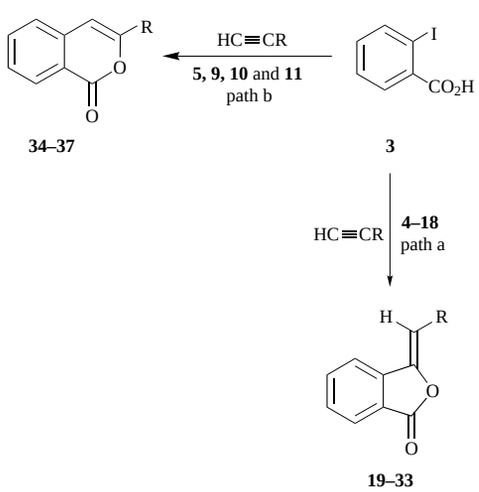
2

plants,[2] celery-oil constituents, odour principles of celery leaf and stem and celery brandy[3–6] and as the constituents of the dried rhizome of *Lingusticum wallichi*, commonly known as 'Senkyu' in Japan[7] and of *Cnidium* rhizome (chuan-xing) in Korea used in the treatment of anaemia and women's disease[8] is known. Phthalide-isoquinoline alkaloids have been described by Manske.[9] The biological activities of 3-alkylidenephthalides as antispasmodic, herbicidal and insecticidal agents,[10] as pesticides[11] and cytotoxic agents[12] have been described by different investigators. 3-Arylidene- or -alkylidene-phthalides have also been used extensively as intermediates for the synthesis of various drugs[13–16] and naturally occurring compounds.[17–21]

Over a period of more than a hundred years, a number of methods have been developed for the synthesis of 3-arylidene- or 3-alkylidene-phthalides and phthalide-containing natural products. These can be classified in the following categories: (i) a high-temperature method[22,23] originally developed by Gabriel which involved the reaction of phthalic anhydride with acetic anhydride or an arylacetic acid at 230–250 °C; (ii) base-catalysed condensation[24–26] of phthalides with aldehydes; (iii) a Wittig–Horner-type condensation of aromatic aldehydes and phthalide phosphonates;[27,28] (iv) condensation of an *o*-halogenobenzoic acid with copper(I) acetylides (Castro reaction).[29] Various modifications of the above reactions have also been described.[30–33] The synthesis of 3-alkylidenephthalides from photochemical rearrangements of substituted indane-1,3-diones and electrochemical reduction of phthaloyl dichloride has been reported.[34,35]

For the last few decades palladium-catalysed reactions[36] have been of great significance in carbon–carbon bond formation and have been widely used for carboannulation[37] and heteroannulation[38] processes. However, palladium-catalysed methods for the synthesis of phthalides are limited in number. Thus, Hegedus and co-workers[39] have reported the palladium-assisted cyclisation of 2-vinylbenzoic acid and 2-(2-methylprop-2-enyl)benzoic acid leading to 2-substituted phthalides in low yields. However, the reactions needed a stoichiometric amount of the palladium reagent. The thallation–olefination of benzoic acid in the presence of catalytic amounts of palladium reagents usually led to isocoumarins, although phthalides were obtained in a few cases.[40] A two-step synthesis of 3-ylidenephthalides involving palladium-catalysed coupling of alkynes with an *o*-(iodomethyl)benzoate followed by cyclisation has been reported.[41] However, the synthesis of only two phthalides by this route has been described. Recently, a few phthalides in low yields, the major products being the corresponding isocoumarins, were reported from the palladium-catalysed condensation of terminal acetylenes with *o*-iodobenzoic acid in the presence of zinc chloride.[42]

In connection with our studies[1,43–45] on the synthesis of various heterocyclic structures through palladium-catalysed reaction of terminal alkynes, we became interested in the palladium-catalysed heteroannulation of *o*-iodobenzoic acid. In this paper, we report a very convenient and general method for the heteroannulation of *o*-iodobenzoic acid **3** with terminal alkynes **4**–**18** under palladium catalysis conditions which led to the phthalides **19**–**33** as major products (Scheme 1, path a) and to the isocoumarins **34**–**37** as minor products (Scheme 1, path b).



Scheme 1 Groups R are defined in Table 1

Results and discussion

The reactions were usually carried out by heating a mixture of 2 mol equiv. of *o*-iodobenzoic acid **3** and 4 mol equiv. of acetylenic compounds **4**–**18** in the presence of 0.07 mol equiv. of palladium catalyst, 0.2 mol equiv. of copper(I) iodide and 2 mol equiv. of a base in dimethylformamide (DMF) as solvent. The results are summarised in Table 1.

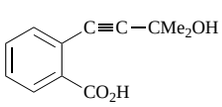
Usually the reaction was carried out at 60 °C for 16 h. The use of lower temperatures, *e.g.* room temperature, led to lower yields of products. It was found that with the use of phase-transfer catalyst (PTC), *e.g.* Bu_4NCl in DMF in the presence of KOAc or K_2CO_3 as base, the reaction (entry 6) could be carried out at room temp. However, in addition to the mixture of the

Table 1 Palladium-catalysed heteroannulation of *o*-iodobenzoic acid **3** with terminal alkynes **4**–**18** leading to phthalides **19**–**33** and isocoumarins **34**–**37** (Scheme 1)

Entry	Alkyne (R)	Catalyst	Solvent/Base	Conditions (T/°C; t/h)	Products (phthalides + isocoumarins)	Yield[c] (%)
1	**4** (H)	$(Ph_3P)_2PdCl_2$, CuI	MeCN, Et_3N, NaHCO	60; 48	**19**	27
2[a]	**5** (Ph)	$(Ph_3P)_2PdCl_2$, CuI	MeCN, Et_3N	room temp.; 48	**20** + **34** (6:4)	36
3	**6** (C_6H_4Cl-*m*)	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**21**	68
4	**7** (1-naphthyl)	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**22**	61
5	**8** (CH_2OH)	$(Ph_3P)_2PdCl_2$, CuI	DMSO, Et_3N	60; 32	**23**	45
6	**9** (CMe_2OH)	$(Ph_3P)_2PdCl_2$, CuI + PTC	DMF, KOAc or K_2CO_3	30; 6	**24** + **35** + **38**	46
7	**9** (CMe_2OH)	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**24** + **35** (4:1)	73
8	**9** (CMe_2OH)	$(Ph_3P)_2PdCl_2$, CuI	DMF–water (2:1), Et_3N	60; 16	**24**	45
9	**9** (CMe_2OH)	$(Ph_3P)_2PdCl_2$, CuI	DMSO, Et_3N	60; 16	**24** + **35** (1:2)	57
10	**9** (CMe_2OH)	$Pd(OAc)_2$, CuI	DMF, Et_3N	60; 16	**24**	61
11	**9** (CMe_2OH)	$Pd(OAc)_2$, CuI + PPh_3	DMF, Et_3N	60; 16	**24**	83
12	**10** (CHOHCH=CHMe)	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**25** + **36**[d] (5:2)	78
13[b]	**11** [CH(OH)Ph]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**26** + **37**[e] (4:1)	40
14	**12** [$CH(OH)C_6H_4Me$-*o*]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**27**	63
15	**13** [$CH(OH)C_6H_4Me$-*p*]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**28**	56
16	**14** [$CH(OH)C_6H_4OMe$-*o*]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**29**	53
17	**15** [$CH(OH)C_6H_4OMe$-*p*]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**30**	51
18	**16** [$CH(OH)C_6H_3(OCH_2O)$-3,4]	$(Ph_3P)_2PdCl_2$, CuI	DMF, Et_3N	60; 16	**31**	64
19	**17** (CO_2Me)	$(Ph_3P)_2PdCl_2$, CuI	MeCN, $NaHCO_3$	60; 32	**32**	69
20	**18** (2,4-dimethoxypyrimidin-5-yl)	$(Ph_3P)_2PdCl_2$, CuI	DMSO, Et_3N	60; 16	**33**	78

[a] When $Pd(OAc)_2$ (5.6 mol%), PPh_3 (5.6 mol%) and CuI (6 mol%) were used in place of bis(triphenylphosphine)palladium(II) dichloride and CuI in MeCN and Et_3N at room temp. for 48 h, the phthalide (11%) was obtained. [b] Using $Pd(OAc)_2$ (5.6 mol%), PPh_3 (5.6 mol%) and CuI (6 mol%) in place of bis(triphenylphosphine)palladium(II) dichloride, the conditions being the same, led to a 30% yield of a mixture of phthalide and isocoumarin in the ratio 2:1. [c] Yields are of chromatographically pure materials. [d] Compound **36** was isolated as a light brown gum; it was identified by IR and ^1H NMR spectra: ν_{max}(neat)/cm^{-1} 1730s and 1650s; δ_H(200 MHz; $CDCl_3$) 1.7 (3 H, d, J 5, CH_3), 5.4 (1 H, m, CHOH), 5.7 (2 H, m, HC=CH), 6.6 (1 H, s, HC=CO), 7.4–7.8 (3 H, m, ArH) and 8.28–8.32 (1 H, m, ArH). [e] Analytically pure compound **37** could not be obtained since compounds **26** and **37** have the same R_f value; product was identified from ^1H NMR spectroscopy: δ_H(200 MHz; $CDCl_3$) 5.6 (1 H, s, CHOH), 6.64 (1 H, s, HC=CO), 7.36–7.8 (3 H, m, ArH) and 8.26–8.32 (1 H, m, ArH).

phthalide **24** and the isocoumarin **35**, an additional product was observed which could be identified as the acyclic product **38** (see under Mechanism sub-section). The latter product was cyclised to the phthalide **24** on being heated in DMF in the presence of Et_3N (entry 7). This indicated that the acyclic product **38** was an intermediate in the formation of the phthalides (see under Mechanism sub-section).



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Catalysts

In general for the heteroannulation of *o*-iodobenzoic acid with alkynes we have used the same catalyst system, *e.g.* $(Ph_3P)_2PdCl_2$ (3.5 mol%) with CuI (6–10 mol%), which we have successfully utilised for the heteroannulation of terminal alkynes to benzofurans.[43] The phthalides were obtained as the major products. However, in some cases the corresponding isocoumarins were obtained as minor products. When $Pd(OAc)_2$ (5 mol%) and copper(I) iodide (5 mol%) were used (entry 10), the phthalide was obtained in 61% yield. Addition of PPh_3 (5 mol%) (entry 11) improved the yield considerably (to 83%). It is of interest to note that the formation of an isocoumarin product was not observed in the latter two cases (entries 10 and 11). The use of $Pd(OAc)_2$ and PPh_3 in other cases led to poorer yields. Thus, in the case of entry 13, a yield of 30% (phthalide : isocoumarin = 2:1), and in case of entry 2, an 11% yield of phthalide, only was obtained.

Solvents and bases

In most cases DMF was found to be the solvent of choice where the maximum yields were obtained. Use of other solvents, *e.g.* DMF–water (2:1), benzene or acetonitrile, led to poorer yields (entry 8). However, other considerations, *e.g.* greater dimerisation of the alkynes in DMF (entries 1, 2, 19), necessitated the use of acetonitrile as the solvent. Also, in the case of entry 5, dimethyl sulfoxide (DMSO) was the solvent of choice since no desired product could be obtained in DMF. Owing to the greater solubility of 5-ethynyl-2,4-dimethoxypyrimidine **18** in DMSO, and also a cleaner reaction product, DMSO was used as the solvent in entry 20. Triethylamine was usually the base of our choice except in a few cases (entries 1 and 19). In the case of entry 1, a mixture of Et_3N (1 mol equiv.) and $NaHCO_3$ (1 mol equiv.) was used to obtain a cleaner product and, in entry 19, $NaHCO_3$ was used since, in the presence of Et_3N, the acetylenic compound **17** reacted with traces of moisture present leading to its loss.[46]

Although in many palladium-catalysed reactions triethylamine has been used both as a base and a solvent, we found that in the case of the synthesis of phthalides from *o*-iodobenzoic acid the use of triethylamine alone led to a heterogeneous mixture, which did not react well. Hence, the use of a solvent like DMF and DMSO is necessary.

Structural variations

A number of alkynes containing a terminal acetylenic moiety were utilised for the heteroannulation process. The carbon–carbon triple bond was attached at the other end to an alkyl, aryl or heteroaryl group. The reaction could take place in fair to excellent yields irrespective of the alkyl or aryl substitution (compare entries 3, 11 and 20). However, phenylacetylene underwent considerable dimerisation[47–49] under the reaction conditions, leading to poor yields of the products (entry 2). Also, acetylene itself was not reactive enough and formed the phthalide **19** in only low yield (entry 1). The reaction was also tolerant of other functional groups present in the alkynes, *e.g.* aromatic chloro (entry 3), hydroxy (entries 5–11), vinyl (entry

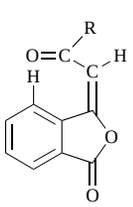
12) and ester (entry 19). Indeed, better yields were obtained with the more substituted alkynes than with the less substituted alkynes (compare entry 5 with entries 7 and 11). Also, when there were olefinic and acetylenic functions present in the same molecule (entry 12), reaction took place at the acetylenic functional group pointing to greater reactivity of the acetylenic moiety over the olefinic moiety.

Regio- and stereo-chemical consequences

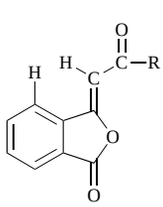
The palladium-catalysed heteroannulation of *o*-iodobenzoic acid with alkynes in the presence of bis(triphenylphosphine)-palladium(II) dichloride and copper(I) iodide in DMF containing triethylamine usually led to the formation of the phthalides **19**–**33** as the major products with the isocoumarins **34**–**37** as the minor products (Table 1). In many cases (entries 1, 3, 4, 8, 10, 11, 14–20), phthalides were found to be the exclusive products whereas the isocoumarin **35** was the major product when the reaction was carried out in DMSO. It is to be noted that Liao and Cheng[42] recently observed that the reaction of *o*-iodobenzoic acid with terminal alkynes in the presence of palladium catalysts and an equivalent amount of zinc chloride led to the isocoumarins as the major products.

All the phthalides and isocoumarins were well characterised by satisfactory spectroscopic (IR, UV and ^{1}H NMR) and analytical data. The phthalides and isocoumarins were differentiated on the basis of the following observations: (i) in the ^{1}H NMR spectra, the vinylic hydrogens of the 3-alkylidenephthalides gave a signal at δ 5.22–6.20, and for the 3-arylidenephthalides at δ 6.36–7.06; however, for the corresponding isocoumarins, the vinylic proton signals were between δ 6.59–6.90, with the vinylic proton of the phthalides usually being 0.5–0.7 ppm to higher field than the corresponding protons of the isocoumarins; (ii) in some cases, the vinylic proton of the phthalides **25**–**31** appeared as a doublet due to coupling with the vicinal protons whereas the vinylic protons (at C-4) of the isocoumarins always appeared as a singlet; (iii) in the IR spectra, the phthalides absorbed in the range 1785–1770 cm^{-1} due to the carbonyl of the 5-membered lactone ring, whereas in the isocoumarins the carbonyl frequency for the six-membered lactone ring was observed at 1750–1730 cm^{-1}. Our observations were in full agreement with those reported by other workers.[23,29,32,39,42,50]

The heteroannulation process was found to be completely stereospecific since only the *Z*-isomers were obtained. The stereochemistry was based on the chemical shifts of the vinylic protons, in the *Z*-isomers, the vinylic proton chemical shift being at a somewhat higher field compared with that of the *E*-isomers[23,32] where the vinylic proton was deshielded due to the lactone oxygen atom. Also, in compound **32** the aromatic

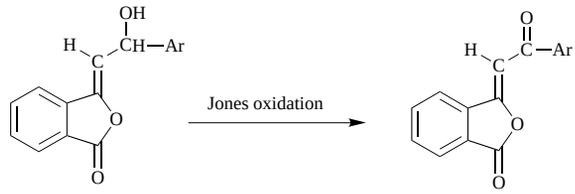


(*E*)-**32** R = OMe
(*E*)-**39** R = Ph



(*Z*)-**32** R = OMe
(*Z*)-**39** R = Ph

proton at carbon-4 was considerably deshielded due to proximity with the carbonyl group in the *E*-isomer[32] and hence appeared at δ 9.0 whereas other aromatic protons appeared in the region δ 7.6–7.9. In the case of the *Z*-isomer of compound **32**, all the aromatic protons appeared in the region δ 7.7–8.1 because of the absence of such deshielding due to the carbonyl group. From a comparison of the chemical shifts, the compound synthesised through palladium-catalysed reactions was shown to be the *Z*-isomer. Also, compounds **26** and **27** were



26
27

26, 39, Ar = C_6H_5
27, 40, Ar = C_6H_4Me-*o*

39
40

Scheme 2

oxidised to the corresponding ketones **39** and **40** respectively (Scheme 2).

From an examination of the ^{1}H NMR spectra of compounds **39** and **40** and a comparison with that of (*E*)-3-(2′-oxo-2′-phenylethylidene)phthalide,[32] compounds **39** and **40** were assigned the *Z*-configuration. Hence, compounds **26** and **27** synthesised through the palladium-catalysed reactions have the *Z*-configuration. The *Z*-isomer of compound **20** was not converted into the *E*-isomer or the corresponding isocoumarin **34** when substrate **20** was treated under the usual conditions.

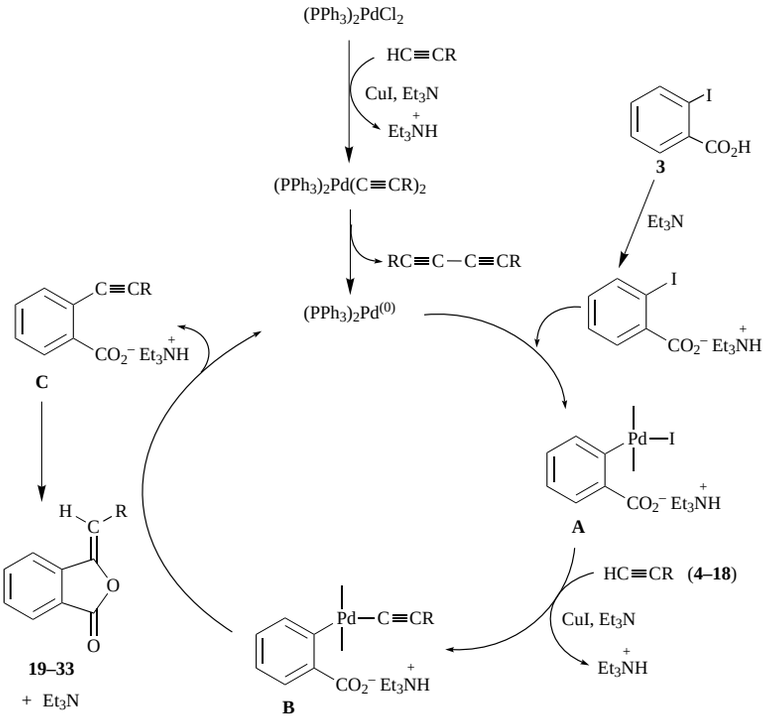
Mechanism

The mechanism of the reaction can be envisaged to proceed according to Scheme 3.

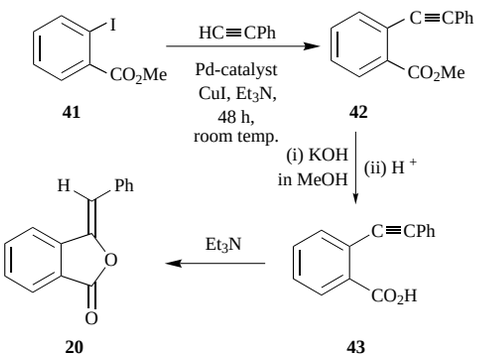
The reaction of *o*-iodobenzoic acid **3** with alkynes **4**–**18** took place in the presence of bis(triphenylphosphine)palladium(II) dichloride and copper(I) iodide. It was observed that in the absence of palladium catalyst no reaction took place, whereas in the absence of copper(I) iodide only traces of the cyclised products were obtained. Thus, both palladium catalyst and copper(I) iodide were essential for the success of this reaction. It could be suggested that Pd^0 must be the intermediate involved in the catalytic process as originally proposed by Hagihara and co-workers[47] in the arylation of acetylenes. The formation of the dimers of the alkynes, *e.g.* R-(C≡C)$_2$R [R = Ph, -CMe$_2$(OH)], under the reaction conditions supports the above mechanism. Similar dimerisation of terminal alkynes has also been previously noticed[48,49] in the presence of bis(triphenylphosphine)-palladium(II) dichloride. The Pd^0 underwent oxidative coupling with the triethylammonium salt of *o*-iodobenzoic acid to yield the palladated complex **A** which on cross-coupling with the copper(I) acetylides derived from the alkynes and copper(I) iodide in the presence of triethylamine, led to the aryl-(alkynyl)palladium species **B**. This on extrusion of Pd^0 led to the formation of the alkynylated compounds **C** which underwent cyclisation to the phthalides **19**–**33**. An open-chain compound, *o*-(2-phenylethynyl)benzoic acid **43**, could be obtained by palladium-catalysed condensation of phenylacetylene with methyl *o*-iodobenzoate **41** and subsequent alkaline hydrolysis of the intermediate compound **10** (Scheme 4).

o-(2-Phenylethynyl)benzoic acid **43** could be cyclised exclusively to the corresponding phthalide **20** (30%) by treatment with triethylamine in acetonitrile at room temp. The presence of copper(I) iodide increased the yield (45%) to some extent whereas the palladium(II) catalyst did not affect the cyclisation process very much. It appears that the cyclisation was catalysed principally by the conjugate acid of triethylamine with some assistance from the copper(I) ion. The cyclisation of the acyclic compound might yield a five-membered aromatic lactone with exocyclic double bond (3-ylidynephthalide) or a six-membered aromatic lactone with the double bond in the *endo* position (isocoumarin). Since the formation of the five-membered ring was easier than that of the six-membered ring, the phthalides were obtained as major products (Scheme 5).

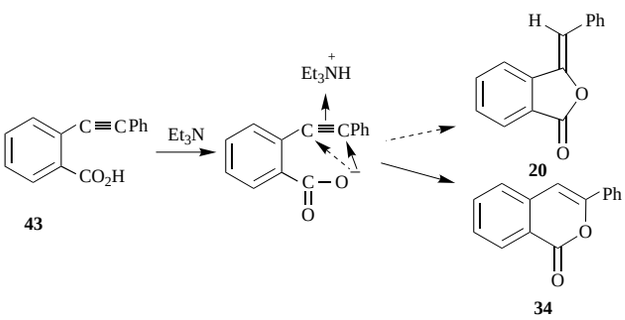
It was found that the 3-ylidenephthalides were obtained in good yields even if the work-up procedure was carried out



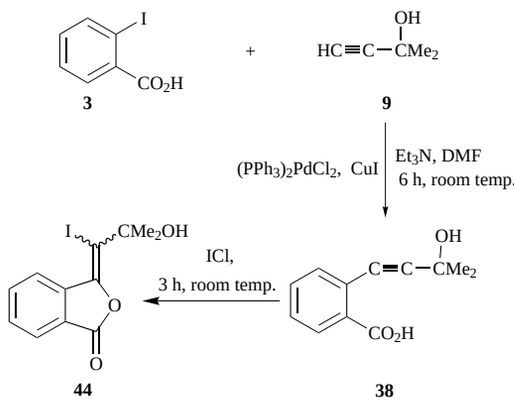
Scheme 3



Scheme 4



Scheme 5



Scheme 6

using aq. $NaHCO_3$ instead of acid. Furthermore, the reaction of entry 20 needed no acid or base work-up procedure after completion of the reaction. The product **33** appeared as a solid in the reaction mixture and could readily be obtained after filtration, confirming that the cyclisation process was affected by the conjugate acid of triethylamine. Further confirmation of the acyclic compound **38** as an intermediate was obtained by the isolation of 3-(1′-iodo-2′-hydroxy-2′-methylpropylidene)-phthalide **44** from the reaction of *o*-iodobenzoic acid with dimethylprop-2-ynyl alcohol when IC1 was added after 6 h (Scheme 6).

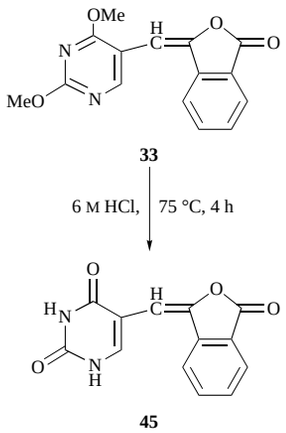
Our observations on the cyclisation of the alkynoic acids to the phthalides in triethylamine is in contrast to those of Liao and Cheng[42] who found that the cyclisation of the alkynoic acid in Et_3N in the presence of $ZnCl_2$ yielded the isocoumarins.

Conclusions

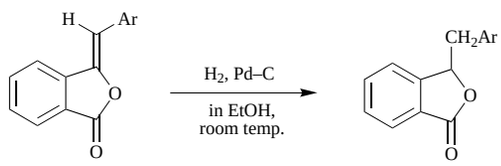
The methodology we have developed for the synthesis of the phthalides was utilised by us for the synthesis of a number of phthalide-containing structures of biological significance. Thus, compound **33** was demethylated with 6 M hydrochloric acid to afford a uracil derivative **45** with a phthalide structure at C-5 (Scheme 7).

Also, 3-benzylidene- and 3-naphthylidene-phthalides were the precursors of indane-1,3-diones[13] and indones[24b] which have significant biological activities. 3-Benzylidenephthalide also exhibited cytotoxic activity against P388 leukaemia cells in culture.[12] The chloro derivative of 3-benzylidenephthalide, compound **21**, has been utilised for the synthesis of 2,3 : 6,7-dibenzosuberan[51] which has sedative, anticholinergic, antispasmodic and antihistaminic activities. The corresponding acid of the ester **32** was found to be the precursor of phthalazineacetic acid and ester derivatives which are novel intermediates for aldose reductase inhibitors.[14] The alkylidenephthalides could be reduced to the corresponding saturated phthalides (Scheme 8), making the process amenable to the synthesis of naturally occurring phthalide-containing alkaloids.[24a]

We have described a successful palladium-catalysed reaction



Scheme 7



5, 46 Ar = C_6H_4Cl-*m*
6, 47 Ar = Ph

Scheme 8

for the synthesis of phthalides from readily available starting materials. The method is easy to carry out, proceeds under relatively mild conditions, is catalytic in palladium reagents, and does not involve any toxic reagents. The process is also amenable to the synthesis of various phthalide-containing naturally occurring substances and compounds of biological interest.

Experimental

Mps were determined in an open sulfuric acid bath or on a Reichert (285980) (Austria) bath and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrometer for solutions in spectrophotometric grade ethanol (Baker). IR spectra were taken on a Perkin-Elmer 298 instrument for samples as KBr plates or liquid films. ^{1}H NMR spectra were recorded on a Varian EM-360, a Varian XL-200 or a Bruker DPX-300 spectrometer for samples in solvents as indicated with tetramethylsilane as internal reference; *J* values given in Hz. Silica gel TLC was performed on 60F-254 precoated 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. Arylacetylenes[52] **6** and **7** and acetylenic alcohols[53] **9**–**16** were synthesised according to literature procedures. Phenylacetylene **5**, prop-2-ynyl alcohol **8** and methyl propiolate **17** were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, USA. *o*-Iodobenzoic acid **3** was synthesised according to literature procedures.[54] 5-Ethynyl-2,4-dimethoxypyrimidine **18** was synthesised according to the literature method.[55] All the phthalides synthesised have the *Z*-configuration.

General procedure for the synthesis of phthalides and isocoumarins

A mixture of *o*-iodobenzoic acid **3** (2 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.07 mmol), copper(I) iodide (0.20 mmol) and triethylamine (2 mmol) was stirred in DMF (5 cm^3) under nitrogen for 1 h. The acetylenic compound (4 mmol) was then added, and the mixture was stirred at room temp. for 1 h and then was heated at 60 °C for the time indicated in the Table 1. At the end of the reaction, the DMF was removed under reduced pressure and the residue was extracted with chloroform (3 × 50 cm^3). The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (2 × 25 cm^3) followed by water (3 × 50 cm^3) and dried (anh. Na_2SO_4). The crude product obtained after removal of solvent was purified by column chromatography on silica gel, using 1 : 1 light petroleum (distillation range 60–80 °C)–chloroform as eluent.

3-Methylenephthalide 19

To a mixture of *o*-iodobenzoic acid **3** (0.25 g, 1 mmol), triethylamine (0.2 g, 2 mmol) and sodium hydrogen carbonate (0.17 g, 2 mmol) in acetonitrile (3 cm^3) were added bis(triphenylphosphine)palladium(II) dichloride (0.024 g, 0.035 mmol) and copper(I) iodide (0.01 g, 0.1 mmol) under oxygen-free argon. Then acetylene gas **4** was introduced to this mixture and stirring was continued for 48 h at 60 °C. The mixture was poured into water (100 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (50 cm^3) followed by water (3 × 50 cm^3). The crude product obtained after removal of solvent was purified by column chromatography on silica gel, using 1 : 1 chloroform–light petroleum as eluting solvent; mp 57–58 °C (lit.,[56] 57 °C); ν_{max}(KBr)/cm^{-1} 1780s, 1735s and 1665s; δ_H(300 MHz; $CDCl_3$) 5.22 (2 H, s, C=C*H*$_2$), 7.55–7.59 (2 H, m, ArH), 77.1 (1 H, d, *J* 6, ArH) and 7.885 (1 H, d, *J* 9, ArH); δ_C(75 MHz; $CDCl_3$) 91.279 (C=*C*H$_2$), 120.560, 124.969, 125.181, 130.417, 134.451, 138.896, 151.726 and 166.845 (CO); δ_C(75 MHz; $CDCl_3$; DEPT 135) 91.471 (inverted, C=*C*H$_2$), 120.749, 125.370, 130.606 and 134.641.

3-Benzylidenephthalide 20

To a mixture of *o*-iodobenzoic acid **3** (0.25 g, 1 mmol) and triethylamine (0.2 g, 2 mmol) in acetonitrile (3 cm^3) were added bis(triphenylphosphine)palladium(II) dichloride (0.024 g, 0.035 mmol) and copper(I) iodide (0.019 g, 0.1 mmol) under oxygen-free argon. To the stirred mixture was added phenylacetylene **5** (0.2 g, 2 mmol) carefully and the mixture was stirred at room temp. for 48 h. After usual work-up, the crude residue was purified by column chromatography over silica gel, using 1 : 1 chloroform–light petroleum as eluting solvent. 3-Benzylidenephthalide **20** was obtained in the earlier fractions; mp 103–104 °C (lit.,[22b] 100–101 °C); ν_{max}(KBr)/cm^{-1} 1775s; δ_H(300 MHz; $CDCl_3$) 6.42 (1 H, s, HC=C), 7.32–7.45 (3 H, m, ArH), 7.54 (1 H, t, *J* 7.5, ArH), 7.7–7.79 (3 H, m, ArH), 7.85 (1 H, d, *J* 7.8, ArH) and 7.93 (1 H, d, *J* 7.8, ArH); δ_C(75 MHz; $CDCl_3$) 107.026, 119.769, 123.287, 125.483, 128.364, 128.709, 129.721, 130.064, 133.012, 134.446, 140.517, 144.492 and 167.041 (CO); δ_C(75 MHz; $CDCl_3$; DEPT 135) 107.219, 119.961, 125.674, 128.556, 128.900, 129.913, 130.256 and 134.639. 3-Phenylisocoumarin **34** was obtained in the latter fractions; mp 79–80 °C (lit.,[50] 86–86.5 °C); ν_{max}(KBr)/cm^{-1} 1740s and 1665s; δ_H(60 MHz; CCl_4) 6.9 (1 H, s, HC=C), 7.27–7.93 (8 H, m, ArH) and 8.3 (1 H, m, ArH).

3-(*m*-Chlorobenzylidene)phthalide 21

This was synthesised according to the general procedure; crude product was crystallised from aq. methanol, mp 148–150 °C (Found: C, 70.65; H, 3.66. $C_{15}H_9ClO_2$ requires C, 70.18; H, 3.53%); ν_{max}(KBr)/cm^{-1} 1785s and 1650s; λ_{max}(EtOH)/nm 336 (log ε 4.25), 306 (4.22), 294 (4.24) and 244 (4.11); δ_H(300 MHz; $CDCl_3$) 6.36 (1 H, s, HC=C), 7.28–7.38 (2 H, m, ArH), 7.56–7.62 (1 H, m, ArH), 7.73–7.84 (4 H, m, ArH) and 7.96 (1 H, d, *J* 7.5, ArH).

3-(α-Naphthylmethylene)phthalide 22

This was prepared according to the general procedure, and was crystallised from aq. methanol; mp 137–138 °C (Found: C, 84.19; H, 4.49. $C_{19}H_{12}O_2$ requires C, 83.80; H, 4.44%);

ν_{max}(KBr)/cm^{-1} 1770s and 1650s; λ_{max}(EtOH)/nm 361 (log ε 4.23) and 261 (4.13); δ_H(60 MHz; $CDCl_3$) 7.06 (1 H, s, HC=C) and 7.33–8.36 (11 H, m, ArH). An (α-naphthylmethylene)-phthalide (mp 179 °C) of unspecified stereochemistry has been reported.[24b]

3-(2′-Hydroxyethylidene)phthalide 23
This was crystallised from light petroleum, mp 95–96 °C (lit.,[29] 96.5–98.5 °C) (Found: C, 68.38; H, 4.77. $C_{10}H_8O_3$ requires C, 68.18; H, 4.58%); ν_{max}(KBr)/cm^{-1} 1780s, 1685s and 1610s; λ_{max}(EtOH)/nm 309 (log ε 3.6), 260 (4.09) and 233 (4.14); δ_H(100 MHz; $CDCl_3$) 4.6 (2 H, d, CH_2OH), 5.83 (1 H, t, HC=C) and 7.48–7.96 (4 H, m, ArH).

3-(2′-Hydroxy-2′-methylpropylidene)phthalide 24
This was crystallised from light petroleum, mp 91–92 °C (Found: C, 70.86; H, 6.03. $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%); ν_{max}(KBr)/cm^{-1} 1785s, 1730s and 1680s; λ_{max}(EtOH)/nm 311 (log ε 3.75), 261 (4.23) and 237 (4.24); δ_H(200 MHz; $CDCl_3$) 1.58 (6 H, s, CH_3), 2.64 (1 H, br, OH), 5.86 (1 H, s, HC=C), 7.76–7.94 (3 H, m, ArH) and 7.94–7.98 (1 H, m, ArH).

3-(2′-Hydroxy-2′-methylethyl)isocoumarin 35
This was obtained as a major product from the reaction of *o*-iodobenzoic acid **3** (2 mmol) and dimethylprop-2-ynyl alcohol **9** by carrying the reaction in DMSO instead of DMF and triethylamine; *compound* **35** was crystallised from light petroleum, mp 70–72 °C (Found: C, 70.74; H, 6.29. $C_{12}H_{12}O_3$ requires C, 70.50; H, 5.92%); ν_{max}(KBr)/cm^{-1} 1735s, 1720s and 1655s; λ_{max}(EtOH)/nm 323 (log ε 3.53), 273 (3.83), 265 (3.94), 258 (3.88) and 241 (4.15); δ_H(100 MHz; $CDCl_3$) 1.56 (6 H, s, 2′-CH_3), 3.52 (1 H, s, OH), 6.59 (1 H, s, HC=C), 7.26–7.66 (3 H, m, ArH) and 8.06–8.19 (1 H, m, ArH).

3-(2′-Hydroxypent-3′-enylidene)phthalide 25
This was synthesised from *o*-iodobenzoic acid **3** and 3-hydroxyhex-4-en-1-yne **10** according to the general procedure. After usual work-up, the crude product was purified by column chromatography with chloroform as eluting solvent. A mixture of the phthalide **25** and the isocoumarin **36** in the ratio 5:2 as indicated by the ^{1}H NMR spectrum was isolated. The phthalide was further purified by preparative TLC (PLC) on silica gel. A light yellow gum was obtained, which was found to be light sensitive and became a dark brown gum on storage for several hours. *Compound* **25** had (Found: C, 72.41; H, 6.04. $C_{13}H_{12}O_3$ requires C, 72.22; H, 5.6%); ν_{max}(KBr)/cm^{-1} 1780; δ_H(200 MHz; $CDCl_3$) 1.74 (3 H, d, *J* 5, CH_3), 2.06 (1 H, br, OH), 5.45 (1 H, m, C*H*OH), 5.70 (2 H, m, HC=CH), 5.86 (1 H, d, *J* 6, HC=CO), 7.58–7.8 (3 H, m, ArH) and 7.94–7.98 (1 H, m, ArH). 3-(1′-Hydroxybut-2′-enyl)isocoumarin **36** was identified by the ^{1}H NMR spectrum (see footnote *d*, Table 1).

3-(2′-Hydroxy-2′-phenylethylidene)phthalide 26
This was synthesised from *o*-iodobenzoic acid **3** (0.5 g, 2 mmol) and 1-phenylprop-2-yn-1-ol **11** (0.3 g, 3 mmol) according to the general procedure. The crude product was purified by column chromatography followed by PLC. The pure *phthalide* **26** was obtained as a solid by crystallisation from light petroleum, mp 111–112 °C (Found: C, 76.14; H, 4.80. $C_{16}H_{12}O_3$ requires C, 76.18; H, 4.80%); ν_{max}(KBr)/cm^{-1} 1760s and 1690s; λ_{max}(EtOH)/nm 310 (log ε 3.78), 263 (4.19) and 237 (4.19); δ_H(200 MHz; $CDCl_3$) 2.6 (1 H, OH), 5.88 (1 H, d, *J* 9, CHOH), 6.12 (1 H, d, *J* 9, HC=C), 7.36–7.80 (8 H, m, ArH) and 7.96–8.0 (1 H, m, ArH). After crystallisation of the phthalide **26**, the mother liquor was concentrated and dried to obtain a yellow gum which was found to be mostly 3-(1′-hydroxy-1′-phenylmethyl)-isocoumarin **37**, identified by ^{1}H NMR spectroscopy (see footnote *e*, Table 1).

3-[2′-Hydroxy-2′-(*o*-tolyl)ethylidene]phthalide 27
This was prepared from *o*-iodobenzoic acid **3** (0.5 g, 2 mmol) and 1-(*o*-tolyl)prop-2-yn-1-ol **12** (0.44 g, 3 mmol) using the general procedure. The crude product was purified by column chromatography, followed by PLC and then crystallisation from light petroleum to yield the *phthalide* **27** as a light yellow gum (Found: C, 76.40; H, 5.68. $C_{17}H_{14}O_3$ requires C, 76.67; H, 5.30%); ν_{max}(neat)/cm^{-1} 1785s, 1685s and 1610s; λ_{max}(EtOH)/nm 310 (log ε 3.79), 264 (4.15) and 236 (4.18); δ_H(100 MHz; $CDCl_3$) 2.25 (3 H, s, CH_3), 2.7 (1 H, br s, CHO*H*), 5.78 (1 H, d, *J* 9, C*H*OH), 6.20 (1 H, d, *J* 9, HC=C), 7.16–7.28 (4 H, m, ArH), 7.5–7.72 (3 H, m, ArH) and 7.88–7.96 (1 H, m, ArH).

3-[2′-Hydroxy-2′-(*p*-tolyl)ethylidene]phthalide 28
This was synthesised according to the general procedure, using the alcohol **13**. The crude product was purified by column chromatography (silica gel 60–120 mesh with 5% ethyl acetate in chloroform as eluent) and then PLC; *compound* **28** was obtained as a light yellow gum (300 mg, 56%) (Found: C, 76.43; H, 5.33. $C_{17}H_{14}O_3$ requires C, 76.67; H, 5.30%); ν_{max}(neat)/cm^{-1} 1785s and 1690w; λ_{max}(EtOH)/nm 309 (log ε 3.83), 265 (3.90) and 232 (4.10); δ_H(300 MHz; $CDCl_3$) 2.32 (3 H, s, ArCH_3), 2.67 (1 H, br s, CHO*H*), 5.815 (1 H, d, *J* 9, C*H*OH), 6.00 (1 H, d, *J* 9, C=CH), 7.16 (2 H, d, *J* 6, ArH), 7.25–7.68 (5 H, m, ArH) and 7.86 (1 H, d, *J* 9, ArH); δ_C(75 MHz; $CDCl_3$) 21.102, 68.520, 110.193, 120.301, 124.496, 125.791, 126.818, 129.401, 129.577, 130.258, 134.483, 137.789, 139.148, 139.393, 145.220 and 180.655; δ_C(75 MHz; $CDCl_3$; DEPT 135) 21.163, 68.577, 110.263, 120.363, 125.472, 125.854, 126.883, 129.463, 129.640, 130.318 and 134.547.

3-[2′-Hydroxy-2′-(*o*-methoxyphenyl)ethylidene]phthalide 29
This was synthesised according to the general procedure, from the alcohol **14**, purified by chromatography on silica gel (60–120 mesh) (20% ethyl acetate in light petroleum as eluent) and PLC; compound **29** was obtained as a light yellow gum (300 mg, 53%) (Found: C, 72.23; H, 4.78. $C_{17}H_{14}O_4$ requires C, 72.33; H, 4.99%); ν_{max}(neat)/cm^{-1} 1785s, 1685w and 1605w; λ_{max}(EtOH)/nm 312 (log ε 3.79), 265 (4.15) and 219 (4.32); δ_H(300 MHz; $CDCl_3$) 3.31 (1 H, br s, CHO*H*), 3.92 (3 H, s, OCH_3), 6.005 (1 H, d, *J* 9, C*H*OH), 6.09 (1 H, d, *J* 9, C=CH), 6.92 (2 H, d, *J* 6, ArH), 7.26–7.88 (5 H, m, ArH) and 7.89 (1 H, d, *J* 6, ArH); δ_C(75 MHz; $CDCl_3$) 55.405, 66.930, 109.131, 120.269, 124.584, 125.358, 125.822, 127.675, 129.541, 129.691, 130.103, 134.353, 134.748, 139.303, 139.585, 145.293 and 178.015; δ_C(75 MHz; $CDCl_3$; DEPT 135) 55.595, 67.057, 109.355, 120.464, 125.528, 125.914, 127.851, 129.715, 129.861, 130.286 and 134.548.

3-[2′-Hydroxy-2′-(*p*-methoxyphenyl)ethylidene]phthalide 30
This was prepared according to the general procedure from *o*-iodobenzoic acid **3** (500 mg, 2 mmol), 1-(*p*-methoxyphenyl)-prop-2-yn-1-ol **15** (480 mg, 2.96 mmol), bis(triphenylphosphine)palladium(II) dichloride (3 mol%), copper(I) iodide (6 mol%) and triethylamine (600 mg, 6 mmol) in dry DMF (10 cm^3). The crude product was purified by column chromatography on silica gel (60–120 mesh), using 20% ethyl acetate in light petroleum, followed by PLC. *Compound* **30** was obtained as a light yellow gum (290 mg, 51%) (Found: C, 72.09; H, 4.88. $C_{17}H_{14}O_4$ requires C, 72.33; H, 4.99%); ν_{max}(neat)/cm^{-1} 1785s, 1685w and 1605w; λ_{max}(EtOH) 310 (log ε 3.77), 271 (4.20) and 220 (4.34); δ_H(300 MHz; $CDCl_3$) 2.05 (1 H, br s, CHO*H*), 3.87 (3 H, s, OCH_3), 5.86 (1 H, d, *J* 9, C*H*OH), 5.92 (1 H, d, *J* 9, C=C*H*), 6.90 (2 H, d, *J* 6, ArH), 7.26–7.89 (5 H, m, ArH) and 7.91 (1 H, d, *J* 6, ArH); δ_C(75 MHz; $CDCl_3$) 55.481, 66.973, 109.217, 120.383, 124.817, 125.622, 125.819, 127.930, 129.309, 129.807, 130.198, 134.466, 134.826, 139.427, 139.678, 145.405 and 178.235; δ_C(75 MHz; $CDCl_3$; DEPT 135) 55.667, 67.089, 109.427, 120.512, 125.812, 125.973, 128.115, 129.498, 129.984, 130.382 and 134.671.

3-[2′-Hydroxy-2′-(3,4-methylenedioxyphenyl)ethylidene]-phthalide 31
This was synthesised according to the procedure for compound

30, using the alcohol **16**; a thick brown liquid was obtained, which was purified by chromatography on silica gel (60–120 mesh), eluent 15% ethyl acetate in chloroform, and then by PLC; *compound* **31** was obtained as a yellow gum (380 mg, 64%) and was crystallised from diethyl ether–light petroleum as a solid, mp 192–193 °C (Found: C, 68.73; H, 3.87. $C_{17}H_{12}O_5$ requires C, 68.91; H, 4.08%); ν_{max}(KBr)/cm^{-1} 1780s, 1680w and 1610w; λ_{max}(EtOH) 313 (log ε 3.87), 259 (4.18) and 231 (4.38); δ_H(300 MHz; $CDCl_3$) 1.79 (1 H, br s, CHO*H*), 5.76 (1 H, d, *J* 12, C*H*OH), 5.85 (1 H, d, *J* 12, C=CH), 5.96 (2 H, s, OCH_2O), 6.79 (1 H, d, *J* 7.8, ArH), 6.805–7.67 (5 H, m, ArH) and 7.89 (1 H, d, *J* 7.2, ArH).

3-(Methoxycarbonylmethylene)phthalide 32

A mixture of *o*-iodobenzoic acid **3** (0.5 g, 2 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.048 g, 0.07 mmol), copper(I) iodide (0.038 g, 0.2 mmol) and sodium hydrogen carbonate (0.34 g, 4 mmol) was stirred in acetonitrile (4 cm^3) under nitrogen for 1 h. Then methyl propiolate **17** (0.30 g, 4 mmol) was added very slowly and carefully. The mixture was stirred at room temp. for 1 h and then was heated at 60 °C for 32 h. The mixture was poured into water (100 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined organic extracts were washed with distilled water (3 × 50 cm^3), dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The residue obtained on crystallisation from light petroleum afforded the *phthalide* **32** as a solid, mp 156–158 °C (Found: C, 64.64; H, 3.89. $C_{11}H_8O_4$ requires C, 64.70; H, 3.92%); ν_{max}(KBr)/cm^{-1} 1795s, 1720s and 1680s; λ_{max}(EtOH) 320 (log ε 3.69), 308 (3.74), 282 (3.92), 272 (3.99) and 240 (3.97); δ_H(100 MHz; $CDCl_3$) 3.86 (3 H, s, OCH_3), 5.90 (1 H, s, HC=C), 7.7–7.82 (3 H, m, ArH) and 7.96–8.08 (1 H, m, ArH).

3-(2′,4′-Dimethoxypyrimidin-5′-ylmethylene)phthalide 33

A mixture of *o*-iodobenzoic acid **3** (0.5 g, 2 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.048 g, 0.07 mmol), copper(I) iodide (0.038 g, 0.2 mmol) and triethylamine (0.4 g, 4 mmol) was stirred in DMSO (3 cm^3) under oxygen-free argon. Then 5-ethynyl-2,4-dimethoxypyrimidine **18** (0.33 g, 2 mmol) was added and the mixture was stirred at 60 °C for 16 h. A yellow solid separated out from the reaction mixture. This was filtered off, and crystallised from 1 : 1 chloroform–methanol as a light yellow solid; mp 228–230 °C (Found: C, 63.21; H, 4.33; N, 9.62. $C_{15}H_{12}N_2O_4$ requires C, 63.38; H, 4.26; N, 9.86%); ν_{max}(KBr)/cm^{-1} 1785s and 1665s; λ_{max}(EtOH) 349 (log ε 4.32) 319 (4.17), 303 (4.12), 291 (4.13) and 256 (3.98); δ_H(100 MHz; $CDCl_3$) 4.04–4.08 (6 H, d, OCH_3), 6.56 (1 H, s, HC=C), 7.48–7.84 (3 H, m, ArH), 7.92–8.0 (1 H, m, ArH) and 9.16 (1 H, s, 6-H).

3-(Benzoylmethylene)phthalide 39

To an ice-cold solution of 3-(2′-hydroxy-2′-phenylethylidene)-phthalide **26** (0.25 g, 1 mmol) in acetone (15 cm^3) was added Jones reagent dropwise and carefully, and with continuous stirring, until there was no further formation of a green precipitate. The whole mixture was poured into ice–water (3 × 25 cm^3) and extracted with chloroform (3 × 25 cm^3). The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (25 cm^3) and water (2 × 25 cm^3) and dried (anh. sodium sulfate). The residue, obtained after removal of solvent, was crystallised from light petroleum, mp 163–164 °C (lit.,[32] 168 °C) (20%); ν_{max}(KBr)/cm^{-1} 1790s, 1655s and 1615s; δ_H(60 MHz; $CDCl_3$) 6.75 (1 H, s, =CHCO) and 7.4–8.2 (9 H, m, ArH).

3-(*o*-Toluoylmethylene)phthalide 40

This was synthesised from 3-[2′-hydroxy-2′-(*o*-tolyl)ethylidene]-phthalide **27** by oxidation with Jones reagent according to the procedure described under compound **39**; *compound* **40** was obtained as a pale yellow gum (43%) (Found: C, 77.43; H, 4.59. $C_{17}H_{12}O_3$ requires C, 77.27; H, 4.54%); ν_{max}(neat)/cm^{-1} 1790s, 1720s and 1610s; δ_H(60 MHz; $CDCl_3$) 2.46 (3 H, s, CH_3), 6.8 (1 H, s, HC=C) and 7.3–8.1 (8 H, m, ArH).

Methyl *o*-(2-phenylethynyl)benzoate 42

This was synthesised by the reaction between methyl *o*-iodobenzoate **41** (1 g, 3.8 mmol) and phenylacetylene **5** (770 mg, 7.62 mmol) in the presence of bis(triphenylphosphine)-palladium(II) dichloride (3 mol%) and copper(I) iodide (8 mol%) in triethylamine (10 cm^3) by stirring at room temp. for 48 h. Title *compound* **42** was obtained as a light brown gum (85%) (Found: C, 81.46; H, 5.31. $C_{16}H_{12}O_2$ requires C, 81.33; H, 5.12%); ν_{max}(neat)/cm^{-1} 2220, 1730 and 1600; λ_{max}(EtOH)/nm 309 (log ε 4.11) and 2.90 (4.27); δ_H(60 MHz; CCl_4) 3.93 (3 H, s, OCH_3) and 7.16–8.09 (9 H, m, ArH).

***o*-(2-Phenylethynyl)benzoic acid 43**

Obtained by the hydrolysis of ester **42** with potassium hydroxide in aq. methanol at room temp. for 24 h; crystallised from diethyl ether–light petroleum; *needle-shaped crystals*, mp 127–128 °C (Found: C, 80.88; H, 4.46. $C_{15}H_{10}O_2$ requires, C, 81.06; H, 4.53%); ν_{max}(KBr)/cm^{-1} 2208, 1695, 1590 and 1575; λ_{max}(EtOH)/nm 304 (log ε 4.24) and 286 (4.34); δ_H(60 MHz; $CDCl_3$) 7.2–8.3 (9 H, m, ArH) and 10.92 (1 H, br s, CO_2H).

3-(2′-Hydroxy-1′-iodo-2′-methylpropylidene)phthalide 44

To a mixture of *o*-iodobenzoic acid **3** (0.5 g, 2 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.048 g, 0.01 mmol), copper(I) iodide (0.038 g, 0.2 mmol) and triethylamine (0.4 g, 4 mmol) in DMF (5 cm^3) under oxygen-free argon was added dimethylprop-2-ynyl alcohol **9** (0.34 g, 4 mmol) and the mixture was stirred at room temp. for 6 h. The mixture was then cooled in an ice-bath and iodine monochloride (0.32 g, 2 mmol) was added very carefully. The mixture was further stirred at room temp. for 3 h. After usual work-up and purification by column chromatography, *iodide* **44** was obtained as a yellow gum (Found: C, 43.69; H, 3.28. $C_{12}H_{11}IO_3$ requires C, 43.63; H, 3.33%); ν_{max}(neat)/cm^{-1} 1775s and 1720w; δ_H(60 MHz; $CDCl_3$) 1.33 (6 H, s, CH_3), 3.3 (1 H, br s, OH) and 7.6–7.98 (4 H, m, ArH).

3-(Uracil-5-ylmethylene)phthalide 45

3-(2′,4′-Dimethoxypyrimidin-5-ylmethylene)phthalide **33** (100 mg) was heated in 6 M hydrochloric acid (3 cm^3) at 75 °C for 4 h. After cooling, the mixture was filtered and the residue was washed carefully with ice-cold water (3 × 5 cm^3); crystallisation from aq. methanol gave *compound* **45** (40 mg, 45%), mp 250 °C (Found: C, 60.57; H, 3.19; N, 10.50. $C_{13}H_8N_2O_4$ requires C, 60.93; H, 3.14; N, 10.93%); ν_{max}(KBr)/cm^{-1} 1765; λ_{max}(DMF)/nm 359 (log ε 4.90) and 336 (4.89); δ_H(300 MHz; [$^2H_6$]DMSO) 6.55 (1 H, s, vinylic H), 7.1–8.1 (5 H, m, ArH and 6′-H), 10.8 (1 H, m, NH) and 11.5 (1 H, s, NH).

Hydrogenation of the phthalides. A typical procedure

A mixture of 3-(*m*-chlorobenzylidene)phthalide **6** (100 mg, 0.39 mmol) was hydrogenated in dry ethanol (15 cm^3) in the presence of Pd–C (10%; 40 mg) at room temp. under atmospheric pressure for 10 h. After usual work-up, a light yellow gum was obtained which was purified by chromatography (silica gel, 1 : 1 light petroleum–chloroform) and crystallisation from diethyl ether–light petroleum to yield 3-(*m*-chlorobenzyl)phthalide **46** as a solid (95 mg, 95%), mp 113–114 °C; ν_{max}(KBr)/cm^{-1} 1750s and 1600w; λ_{max}(EtOH)/nm 282 (log ε 3.14) and 275 (3.2); δ_H(300 MHz; $CDCl_3$) 3.185 (2 H, d, *J* 6.3, ArCH_2), 5.671 (1 H, t, *J* 6.3, OC*H*CH_2), 7.099–7.266 (5 H, m, ArH), 7.512 (2 H, t, *J* 7.5, ArH), 7.642 (2 H, t, *J* 7.5, ArH), 7.856 (1 H, d, *J* 7.5, ArH); δ_C(75 MHz; $CDCl_3$) 40.432 (CH_2), 80.718, 122.054, 125.785, 126.1, 127.348, 127.834, 129.354, 129.637, 129.741, 133.891, 134.231, 137.039, 148.673 and 170.071; δ_C(75 MHz; $CDCl_3$; DEPT 135) 40.614 (inverted), 80.913, 122.251, 125.963, 127.530, 128.025, 129.544, 129.825, 129.928 and 134.089.

3-Benzylphthalide 47

3-Benzylidenephthalide **5** was hydrogenated in the presence of Pd–C (10%) in methanol at room temp. under atmospheric pressure. After usual work-up, solid *product* **7** (90%) was obtained, which was crystallised from diethyl ether–light petroleum, mp 59–60 °C (Found: C, 80.22, H, 5.51. $C_{15}H_{12}O_2$ requires C, 80.33; H, 5.40%); ν_{max}(KBr)/cm^{-1} 1752s and 1600w; λ_{max}(EtOH)/nm 282 (log ε 3.17), 274 (3.18) and 227 (3.96); δ_H(300 MHz; $CDCl_3$) 3.16 (1 H, dd, *J* 14.1 and 6.3, CH_2Ar), 3.29 (1 H, dd, *J* 14.1 and 6.6, CH_2Ar), 5.69 (1 H, t, *J* 6, OC*H*-CH_2Ar), 7.16–7.32 (6 H, m, ArH), 7.49 (1 H, t, *J* 7.5, ArH), 7.604 (1 H, td, *J* 7.5 and 1, ArH) and 7.845 (1 H, d, *J* 7.8, ArH); δ_C(75 MHz; $CDCl_3$) 41.27 (CH_2), 81.624, 122.711, 126.100, 126.662, 127.570, 128.954, 129.603, 130.116, 134.126, 135.411, 149.525 and 170.661; δ_C(75 MHz; $CDCl_3$; DEPT 135) 40.964 (inverted), 81.358, 122.441, 125.800, 127.282, 128.667, 129.327, 129.834 and 133.669.

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