# Synthesis of Phthalides through Palladium-catalysed Heteroannulation of Acetylenic Compounds

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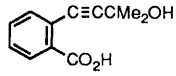
The reaction of *o*-iodobenzoic acid with various acetylenic compounds in the presence of a palladium catalyst leads to phthalides [1-(3*H*)isobenzofuran-3-ones] as major products and isocoumarins as minor products.

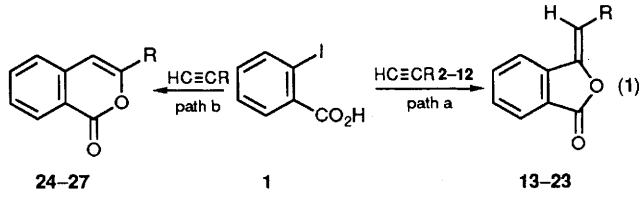
Compounds containing the phthalide nucleus are known to be the constituents of various naturally occurring substances.[1–3] Phthalides have also played an important role as intermediates for the synthesis of several natural products of complex structure.[4] Various methods are known for the synthesis of phthalide-containing structures.[5] Recently, there has been world-wide interest in palladium catalysed carboannulation[6] and heteroannulation reactions.[7] However, the synthesis of phthalide-containing structures from heteroannulation of acetylenic compounds mediated through palladium reagents has not yet been reported.[8]

In view of our interest[9] in potential anticancer and antiviral agents, we became interested in the development of general methods for the synthesis of heterocyclic structures. In palladium-catalysed reactions, acetylenic substrates have been utilized for the synthesis of carbocyclic and heterocyclic structures.[10] In this communication, we report a very convenient and general method for the heteroannulation of acetylenic compounds through palladium-catalysed reactions which lead to the phthalides [1-(3*H*)isobenzofuran-3-ones] as major products [eqn. (1), path a] and to the isocoumarins as minor products [eqn. (1), path b].

**Table 1** Palladium-catalysed heteroannulation of acetylenic compounds **2–12** leading to phthalides **13–23** and isocoumarins **24–27** [eqn. (1)][a]

| Entry | Acetylene | R | Conditions *T*/°C; *t*/h | Solvent | Products[b] Phthalides + Isocoumarins | | | Isolated[c] yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **2** | H | 60; 48 | MeCN | **13** | | | 27 |
| 2 | **3** | Ph | room temp.; 48 | MeCN | **14** | + **24** (6 : 4) | | 30 |
| 3 | **4** | $C_6H_4Cl$-*m* | 60; 16 | DMF | **15** | | | 68 |
| 4 | **5** | 1-Naphthyl | 60; 16 | DMF | **16** | | | 61 |
| 5 | **6** | $CH_2OH$ | 60; 32 | $Me_2SO$ | **17** |  | | 45 |
| 6 | **7** | $CMe_2OH$ | 30; 6 | DMF | **18** | + **25** + **28** | (1 : 1 : 1) | 46 |
| 7 | **7** | $CMe_2OH$ | 60; 16 | DMF[d] | **18** | + **25** (4 : 1) | | 72 |
| 8 | **7** | $CMe_2OH$ | 60; 16 | DMF | **18** | | | 61[e] |
| 9 | **7** | $CMe_2OH$ | 60; 16 | DMF | **18** | | | 85[f] |
| 10 | **7** | $CMe_2OH$ | 60; 16 | $Me_2SO$ | **18** | + **25** (1 : 2) | | 57 |
| 11 | **8** | CH(OH)–CH=CHMe | 60; 16 | DMF | **19** | + **26** (5 : 2) | | 78 |
| 12 | **9** | CH(OH)Ph | 60; 16 | DMF | **20** | + **27** (4 : 1) | | 40[g] |
| 13 | **10** | $CH(OH)C_6H_4Me$-*o* | 60; 16 | DMF | **21** | | | 63 |
| 14 | **11** | $CO_2Me$ | 60; 32 | MeCN | **22** | | | 69[h] |
| 15 | **12** | 2,4-Dimethyoxy-5-pyrimidinyl | 60; 16 | $Me_2SO$ | **23** | | | 78 |

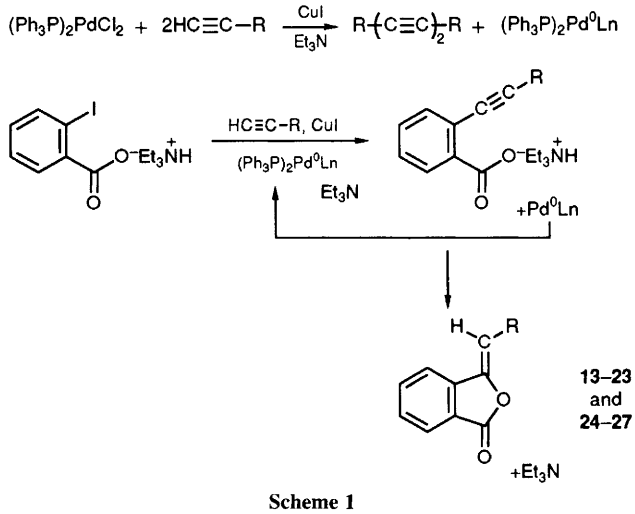
[a] A typical reaction condition: A mixture of *o*-iodobenzoic acid (2 mmol), $(PPh_3)_2PdCl_2$ (0.07 mmol), CuI (0.20 mmol) and triethylamine (2 mmol) was stirred in DMF (5 ml) under nitrogen atmosphere for 1 h. The acetylenic compound (4 mmol) was then added, stirred at room temp. for 1 h. The acetylenic compound (4 mmol) was then added, stirred at room temp. for 1 h and heated at 60 °C for 16 h. [b] Satisfactory spectroscopic (IR, UV and $^1H$ NMR) and analytical data were obtained for all the compounds synthesized. [c] Refers to the yield of phthalide or mixture of products. [d] Other solvents (benzene, MeCN and 1 : 2 ($H_2O$–DMF) were also used (yields 40–45%). [e] $Pd(OAc)_2$ (5 mol%) and CuI (5 mol%) were used as catalysts. [f] $Pd(OAc)_2$ (5 mol%), CuI (5 mol%) and $Ph_3P$ (5 mol%) were used in the reaction. [g] Increase in time gave no improvement in yield. [h] $NaHCO_3$ instead of $Et_3N$ was used as a base.




The reactions were usually carried out by heating a mixture of *o*-iodobenzoic acid **1** and acetylenic compound **2–12** in the presence of a palladium catalyst, copper(I) iodide and a base in dimethylformamide (DMF). The results are shown in Table 1. As can be seen, in most of the cases, the phthalides were obtained in good to excellent yields. In some cases (entries 2, 6, 7, 11 and 12), however, smaller amounts of isocoumarins were also formed. When $Me_2SO$ was used as a solvent in place of DMF, then usually cleaner products resulted, although in one case (entry 10), the isocoumarin was formed as the major component. Acetonitrile was also used in some cases (entries 1, 2 and 14) since the use of DMF in these cases led to greater dimerisation of the acetylenes concerned.

Bis(triphenylphosphine)palladium(II) chloride was found to be the catalyst of choice. The use of other catalysts, *e.g.* $Pd(OAc)_2$, with CuI (entry 8), led to lower yield (61%) of the products. However, addition of triphenylphosphine increased the yield to 85% (entry 9). We have previously used triethylamine as the base. However, in entry 1, a mixture of $Et_3N$ (1 equiv.) and $NaHCO_3$ (1 equiv.) was used to get a cleaner product and in entry 14, $NaHCO_3$ was used since the use of $Et_3N$ led to dimerisation of the acetylenic component. The use of phase-transfer catalysis was also investigated. It was found that with the use of PTC ($Bu_4NCl$) in DMF in the presence of KOAc or $K_2CO_3$ as base, the reaction (entry 7) could be carried out at room temperature also to yield the same mixture of products; however, no improvement in yield was observed.

Various acetylenic substrates were successfully utilised for the heteroannulation reaction and in most cases the yields of the products were fair to excellent. Only in cases where the

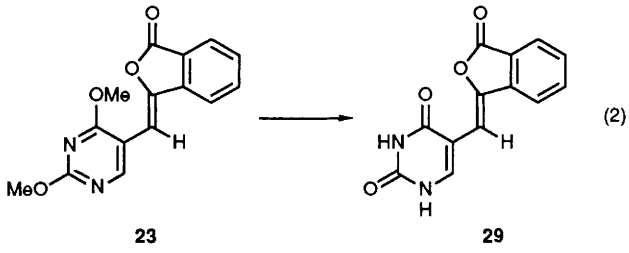



**Scheme 1**

acetylenes were subject to dimerization† (entries 1 and 2), lower yields of products were obtained. The acetylenic compounds used were terminal acetylenes and they were readily available.[11] The acetylenic compounds could also carry various substituents like alkyl, aryl, hydroxy, olefinic, ester and heterocyclic moieties without the heteroannulation process being affected. Indeed, better yields were obtained with more-substituted alkynes than with the less-substituted alkynes. Where olefinic and acetylenic groups were present in the same molecule (entry 11), reaction took place only at the acetylenic end indicating greater reactivity of the acetylenic moiety over the olefinic moiety.

The heteroannulation process has led to the 3-alkylidene phthalides. The process was found to be completely stereospecific since only the *Z*-isomers were obtained.[12] The alkylidene phthalides could be reduced to the corresponding saturated phthalides making the process amenable to the synthesis of naturally occurring phthalide containing alkal-

† The nature of the dimeric products is under investigation.




23 29 (2)

oids.[13] Again, compound **23** was demethylated to a novel 5-substituted uracil derivative **29** of potential biological interest [eqn. (2)].[9] Also, the alkylidene phthalides are precursors to other compounds (indones, indandiones) of biological interest.[14]

The mechanism of the reaction can be envisaged to proceed according Scheme 1.[15,16]‡

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

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‡ Compound **28** was converted mainly to the phthalide either with $(Ph_3P)_2PdCl_2$ (cat.), CuI (cat.), $Et_3N$ in benzene at room temp. for 20 h, or, $(Ph_3P)_2PdCl_2$ (cat.), $NaHCO_3$ in DMF at 60 °C for 12 h, or, $(Ph_3P)_2PdCl_2$ (cat.), $Et_3N$ in benzene at room temp. for 20 h[18] proving compound **28** to be an intermediate towards the phthalide synthesis.