Palladium-catalysed Heteroannulation of Acetylenic Compounds: a Facile Method for the Synthesis of Benzofurans

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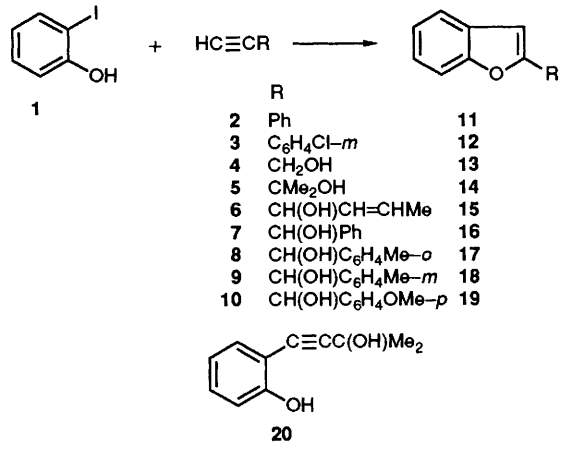
A convenient and general method for the synthesis of benzofurans from *o*-iodophenol and acetylenic compounds under palladium-catalysed conditions is described.

Benzo[*b*]furan derivatives are of interest because of their occurrence in nature[1,2] and their physiological properties.[2] In connection with our studies[3] in the field of biologically active molecules which could be of use as anticancer and antiviral agents, we became interested in the development of general methods for the synthesis of heterocyclic structures. Various methods are known[4] for the synthesis of benzofuran and its derivatives.[5] Recent efforts, however, have centred around the use of palladium catalysts for carbon–carbon bond formation leading to the benzofuran structure. Thus, Larock and coworkers have reported the palladium-promoted cyclisation of *ortho*-substituted aryl allyl ethers to benzofuran derivatives, and the palladium-catalysed heteroannulation of 1,3-dienes leading to 2,3-dihydrobenzofurans.[6] The cyclocarbonylation of 3-furylallyl acetates in the presence of palladium catalysts led to acetoxy benzofurans.[7] Recently a titanium tetrachloride–zinc-mediated intramolecular reductive deoxygenation of *o*-aroyloxy acetophenones to give substituted benzofurans has also been reported.[8]

In palladium-catalysed reactions, acetylenic substrates have been utilised for carbon–carbon bond formation leading to cyclic and polycyclic structures,[9] macrocycles,[10] fulvenes,[11] flavones and chromones,[12] quinoline derivatives,[13] γ-butyrolactones,[14] and indoles.[15] The synthesis of benzofurans from acetylenic substrates under palladium-catalysed reactions has also been reported.[16] We now report a general and convenient method for the heteroannulation of acetylenic compounds leading to benzofuran derivatives. When a mixture of *o*-iodophenol **1** and an acetylenic compound **2–10** was heated in the presence of a palladium catalyst, copper(I) iodide and a base in dimethylformamide, 2-substituted benzofurans were obtained in excellent yield (Table 1) according to Scheme 1. Table 1 shows that $(Ph_3P)_2PdCl_2$ was the best catalyst; other catalysts, *e.g.* $Pd(OAc)_2$ led to lower yields (entries 4 and 9).



Scheme 1

Table 1 Palladium-catalysed heteroannulation of acetylenic compounds leading to benzo[*b*]furan derivatives[a]

Entry	Acetylene[c]	Conditions:[b] *T*/°C; *t*/h	Products[d]	Yield (%)
1	**2**	60; 16	**11**	77
2	**3**	60; 16	**12**	61
3	**4**	60; 16	**13**	68
4	**5**	60; 6	**14**	55
5	**5**	60; 16	**14**	75
6	**5**	Room temp.; 12	**14** + **20** (3 : 7)	38
7	**5**	Room temp.; 24	**14** + **20** (7 : 3)	68
8	**5**	50; 6	**14**	50
9	**5**	60; 6	**14**	20
10	**5**	60; 6	—	—
11	**6**	60; 16	**15**	88
12	**7**	80; 24	**16**	66
13	**8**	80; 24	**17**	73
14	**9**	60; 16	**18**	72
15	**10**	80; 24	**19**	64

[a] Typical reaction; *e.g.* synthesis of **13**; a mixture of *o*-iodophenol (2 mmol), $(PPh_3)_2PdCl_2$ (0.07 mmol), CuI (0.26 mmol) and triethylamine (4 mmol) was stirred in dimethylformamide (5 ml) under nitrogen for 1 h. Prop-2-ynyl alcohol (4 mmol) was added; the mixture was stirred at room temperature for a further 1 h and heated at 60 °C for 16 h. The mixture was then cooled, poured into water (100 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with 5 mol dm^{-3} sodium hydroxide (3 × 100 ml) and water, dried ($MgSO_4$) and purified by chromatography on neutral alumina. [b] *Reagents*: Catalyst, $(Ph_3P)_2PdCl_2$ (entries 1–8, 11–15), $Pd(OAc)_2$ (entries 9 and 10); other reagents, CuI, Et_3N, DMF (entries 1–5, 9, 11–15); CuI, NaOAc, Bu^n_4NCl, DMF (entries 6–8); CuI, Et_3N, PPh_3, DMF (entry 10). [c] Some dimerization of the acetylenic substrates was apparent under the reaction conditions. The nature of the products is under investigation. [d] Satisfactory spectroscopic data (IR, UV and ^1H NMR) were obtained for all the compounds synthesized: typical data, **11**, m.p. 118–120 °C (lit.,[21] m.p. 120.8–121.2 °C); λ_{max}/nm (EtOH) 316, 303, 261 and 226; **15**, colourless oil, λ_{max}/nm (EtOH) 284, 277, and 249; ν_{max}/cm^{-1} 3345, 1660, 1585, 1470 and 1450; δ_H (200 MHz, $CDCl_3$) 1.82 (d, 3H, *J* 4 Hz, CCH_3), 5.34 (d, 1H, *J* 5 Hz, C*H*OH), 5.9–5.94 (m, 2H, CH=CH), 6.68 (s, 1H, ArH-3), 7.24–7.36 (m, 2H, ArH), and 7.52–7.62 (m, 2H, ArH); elemental analyses were satisfactory.

Addition of further PPh_3 completely suppressed the formation of the product (entry 10). Although under the usual conditions, benzofurans were the main products, the use of phase-transfer catalysis (PTC)[17] (Bu^n_4NCl) in dimethylformamide (DMF; entries 6 and 7) at room temperature led to the formation of the acyclic product **20**, which could be the precursor for the benzofuran **14**.† The use of a higher temperature with PTC led to benzofuran **14** as the only product (entry 8).

Thus, we have synthesized a number of 2-substituted benzofurans from readily accessible starting materials[18] under relatively mild conditions and in fair to excellent yields. Some of the synthesised compounds could be easily converted to known natural products[19] or compounds of biological interest.[20]

Financial assistance from the Department of Science and Technology, Government of India, to N. G. K. (Grant No. SP/S1/G-45/88) is gratefully acknowledged. J. S. M. is a J. R. F. under the above project. M. P. thanks the Council of Scientific and Industrial Research, Government of India, for a fellowship.

Received, 24th July 1991; Com. 1/03798F

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† Compound **20** was converted to **14** by treatment with $(Ph_3P)_2PdCl_2$, CuI and triethylamine in DMF at 60 °C.