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PALLADIUM-ASSISTED ORGANIC REACTIONS

VIII *. SIMPLE SYNTHESES OF 2,3-DISUBSTITUTED PHTHALIMIDINES

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Summary

Electron-poor alkenes such as alkyl acrylates have been found to insert into the aromatic carbon–palladium bond in orthobromobenzamides under the conditions of the Heck reaction. For primary and secondary benzamides a further palladium-catalysed reaction occurs to yield 3-substituted, or 2,3-disubstituted phthalimidines.

Introduction

In previous papers in this series [1–6] we have reviewed briefly the preparation, characterisation and some chemical properties of the products of cyclopalladation of benzylamine and benzalimine derivatives, together with interpretations of ^{13}C spectral data [7]. The metal–carbon bonds of such complexes have been shown by us, and by others, to undergo insertion reactions with unsaturated compounds such as electron-poor alkenes, alkynes, styrenes and carbon monoxide.

In our work with the cyclopalladated tertiary benzylamines, further manipulations of the products of insertion to yield heterocyclic compounds [3] met with only limited success, mainly because the ring-closed products were quaternary ammonium compounds which proved to be very difficult to purify and characterise.

Recently [1] we reported a facile synthesis of cyclopalladated primary and secondary benzylamines, but, unfortunately, instead of undergoing insertion reactions with electron-poor alkenes, the products obtained resulted from Michael addition of the benzylamine to the alkene. We have had more success with insertions of carbon monoxide (see below). Parkins et al. have obtained cyclopalladated primary and secondary benzylamines by an alternative method [8] and also describe reactions of the parent compounds with carbon monoxide [9] to yield phthalimidines.

* For Part VII see ref. 1.

Thompson and Heck [10] first described the reaction of cyclopalladated tertiary benzylamines with carbon monoxide to yield phthalimidines with concomitant de-*N*-alkylation. We shall report on aspects of this work elsewhere.

Phthalimidines have been widely studied for a long time (e.g. see Elderfield [11] for an early review). More recently some phthalimidine derivatives have attracted some attention because of their biological activity [12,13]. A number of methods are available for the preparation of phthalimidines, including reduction of phthalimides, reaction of phthalaldehyde with amines, internal ester–amide interchange in *o*-(aminomethyl)benzoic acid esters, and treatment of benzyl cyanides with methanal.

Brunet et al. [14] have synthesised phthalimidine and its *N*-benzyl derivative by reacting 2-bromobenzylamine with CO in a cobalt-catalysed reaction. Most of these methods have been applied to, or are inherently limited to, phthalimidines which are unsubstituted at C(3). Indeed, methods of synthesis which provide C_3-, as well as N-substituted phthalimidines are not well developed. In this paper we describe a "one-pot", palladium-catalysed synthesis of such heterocycles from readily available starting materials.

Experimental

Spectral data (^{1}H and ^{13}C NMR), GC/MS data and microanalytical data were obtained as described previously [2].

Preparation of the phthalimidines **4**. *General method*

A mixture of the bromoamide (10 mmol), acetonitrile (10 ml), triethylamine (12.5 mmol), methyl (or ethyl) acrylate (12.5 mmol), palladium acetate (0.1 mmol) and triphenylphosphine (0.2 mmol) was degassed with N_2, sealed in a glass vial and

TABLE 1

ANALYTICAL DATA FOR THE PHTHALIMIDINES **4**

Compound	Found (calcd.) (%)			M.p. (°C)	Yield (%)
	C	H	N		
4a	60.05 (60.2)	6.35 (6.1)	5.0 (5.0)	125–127	36
4c	67.1 (66.85)	5.85 (5.6)	4.2 (4.1)	137–138	6
4d	67.35 (67.6)	5.7 (6.0)	3.9 (3.9)	113–115	23
4e	58.0 (58.1)	6.0 (6.0)	3.8 (4.0)	120–122	39
4f	58.9 (59.2)	6.2 (6.35)	3.8 (3.8)	155–157	24
4g [a]				142–143	17
4h [b]				oil	66

[a] Confirmed by high resolution mass spec. [b] Small traces of the free aldehydes could not be removed from this compound.

heated at 100°C for 7 d. After cooling the vial was opened and the acetonitrile removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml), the solution washed with dilute NaOH solution, dilute hydrochloric acid and saturated NaCl solution, then dried (Na_2SO_4) and evaporated under reduced pressure to leave an oil. Crystallisation of the oil was achieved with benzene or ethyl ethanoate/hexane. Analytical data are summarised in Table 1.

Preparation of ***3b***

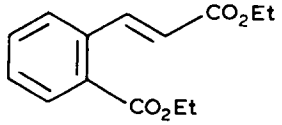
This product of insertion of methyl acrylate into *N*,*N*-diethyl-3,4-dimethoxy-6-bromobenzamide was obtained under the above conditions, m.p. 112°C. ^{1}H NMR, ($CDCl_3$); δ 1.05 (t, *J* 7 Hz, 3H, CH_3), 1.33 (t, *J* 7 Hz, 3H, CH_3), 3.15 (q, *J* 7 Hz, 2H, CH_2), 3.67 (q, *J* 7 Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.35 (d, *J* 16 Hz, 1H, C=CH), 6.81 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.71 (d, *J* 16 Hz, 1H, C=CH). ^{13}C NMR, ($CDCl_3$), δ 12.7 (CH_3), 14.0 (CH_3), 39.1 (CH_2), 43.0 (CH_2), 51.6 (ester, CH_3), 56.1 (OCH_3), 56.1 (OCH_3), 56.1 (OCH_3), 108.6 (aromatic, CH), 109.3 (aromatic, CH), 117.7 (C=C), 123.6 (aromatic C), 131.9 (aromatic C), 141.1 (C=C), 149.4 (aromatic C), 151.1 (aromatic C), 167.1 (C=O), 169.2 (C=O). High resolution mass spectral measurements gave M^+ 321.1582. $C_{17}H_{23}NO_5$ calcd.: M^+ 321.1574.

Preparation of the phthalimidines 7. Example

Carbon monoxide was bubbled through a solution of the complex **6h** (1.5 g) dissolved in chloroform (50 ml) for 30 min at room temperature. The mixture was then heated under reflux for 1 h, cooled, filtered and the filtrate was washed with dilute sodium hydroxide solution, then water and finally saturated sodium chloride. The solvent was removed under reduced pressure and the residue crystallised from chloroform/hexane to yield **7h**. Found: C, 66.7; H, 6.5; N, 6.1. $C_{13}H_{15}NO_3$ calcd.: C, 66.9; H, 6.5; N, 6.0%.

Results and discussion

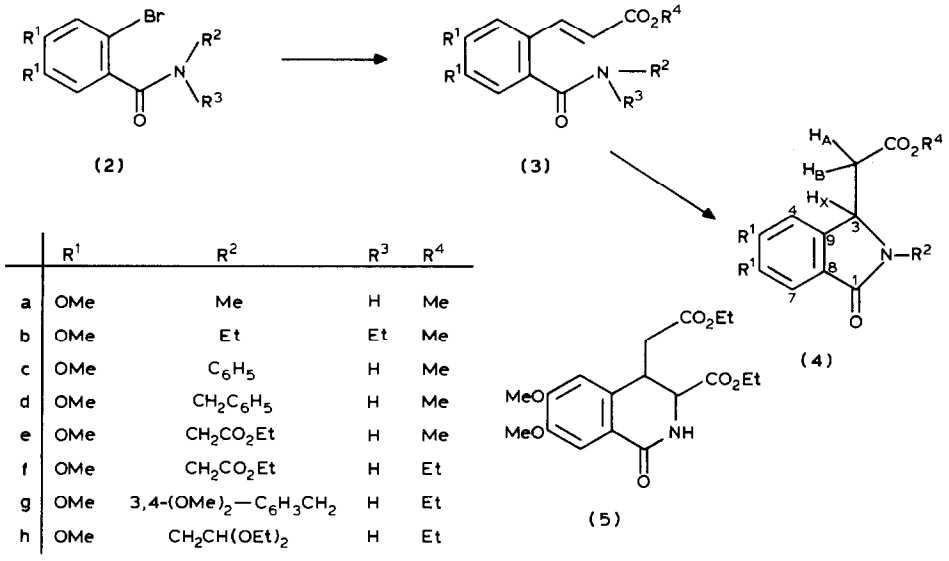
Some time ago Heck et al. described insertion reactions of aromatic compounds into electron-poor alkenes, using catalytic amounts of $PdCl_2$ or $Pd(OAc)_2$. The transient intermediate containing the aromatic carbon–palladium bond was produced, preferably by treating aryl iodides or bromides with the Pd^{II} salt in the presence of triphenylphosphine and the alkene. Much of this work has been reviewed [15,16]. A brief mention was made that ethyl *o*-bromobenzoate reacted with ethyl acrylate under the conditions of the "Heck reaction" to give **1** in good yield [17].



(1)

Whereas we have been unable to repeat this particular reaction, we have found that ring-substituted esters of *o*-bromobenzoic acid work well; these results will be described elsewhere.

We have also found that *o*-bromo-substituted primary, secondary and tertiary benzamides undergo insertion reactions under conditions similar to those used by



	R^1	R^2	R^3	R^4
a	OMe	Me	H	Me
b	OMe	Et	Et	Me
c	OMe	C_6H_5	H	Me
d	OMe	$CH_2C_6H_5$	H	Me
e	OMe	CH_2CO_2Et	H	Me
f	OMe	CH_2CO_2Et	H	Et
g	OMe	3,4-$(OMe)_2$—$C_6H_3CH_2$	H	Et
h	OMe	$CH_2CH(OEt)_2$	H	Et

SCHEME 1

Heck (see Experimental). Thus, when *N*-methyl-3,4-dimethoxy-6-bromobenzamide (**2a**) was treated with 1.25 mol methyl acrylate in acetonitrile solution in the presence of 1.25 mol triethylamine and 1 mole% palladium acetate and 2 mole% triphenylphosphine, a metal-free product was obtained in good yield. That it was not the expected insertion product **3a** was readily apparent from spectral data. In particular, the expected absorptions in the ^1H NMR spectrum for hydrogen atoms attached to the double bond were absent. Instead a typical ABX pattern (300 MHz) was observed between 2.9–5.0δ (see Table 3 for details). By a combination of SFORD and DEPT techniques all of the signals in the ^{13}C NMR spectrum could be assigned (Table 4). No resonances due to sp^2-hybridised carbon atoms (apart from aromatic ring carbon atoms and the C=O group) were found, but methylene and methine carbon absorptions at 38.2 and 56.7δ, respectively, indicated that the compound is the phthalimidine (**4a**), (Scheme 1).

Further confirmation of the structure of **4a** was provided by its mass spectrum. In particular, the ion at *m/z* 206 was shown by metastable mapping to come directly from the molecular ion, presumably by α-cleavage initiated by a radical site on nitrogen:

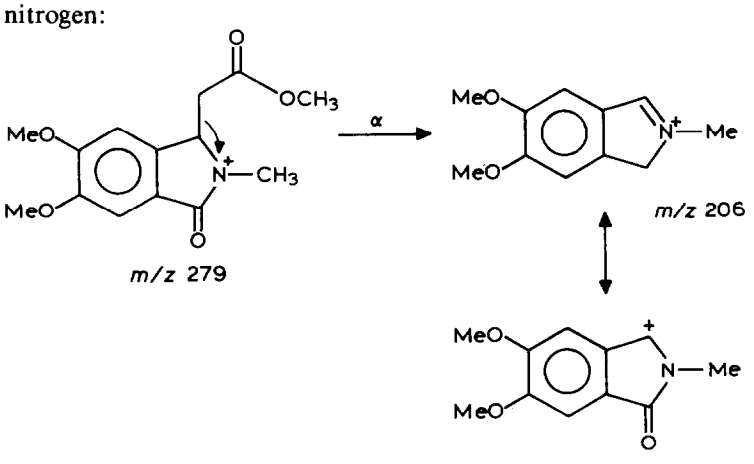
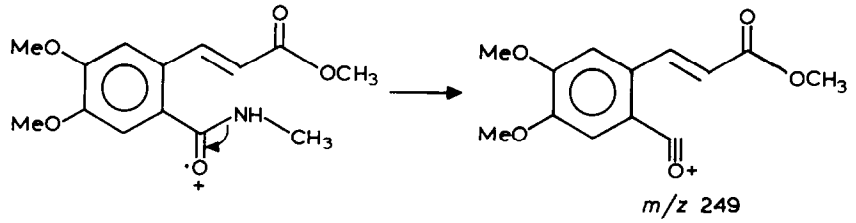


TABLE 2

^{1}H NMR SPECTRAL DATA (δ in ppm; J in Hz)

Compound	H_A	H_B	H_X	CH_3O	ArH	R^2	R^4
4a	2.90	2.63	4.75	3.93 3.94	6.93 7.29	3.10	3.75
4c	2.95	2.46	5.50	3.96 3.96	7.02 7.37	m 7.2–7.6	3.65
4d	2.87	2.57	4.73	3.95 3.90	6.90 7.36	d 4.37, d 5.19 (J 15.5), m 7.2–7.35	3.64
4f	2.83	2.76	5.03	3.94 3.94	6.94 7.32	4.18 1.25 qOR tOR 4.20 (J 7.2) 1.28	4.18 1.25 q OR t OR 4.20 (J 7.2) 1.28
4g	2.87	2.54	4.69	3.92 3.88 3.83 3.81 } 2 of	7.23 7.32	d 4.27 d 5.10 m 6.75–6.8 3.92 (J 15.2)(J 15.2) 3.88 3.83 3.81 } 2 of	q 4.09 t 1.19 (J 7.10)(J 7.10)
4h	3.13	2.58	5.06	3.93 3.93	7.01 7.30	d of d 3.27 (J 6.0) q 4.72 d of d 4.15 (J 4.4) J 14.5	q 4.15 t 1.22 (J 7.16)

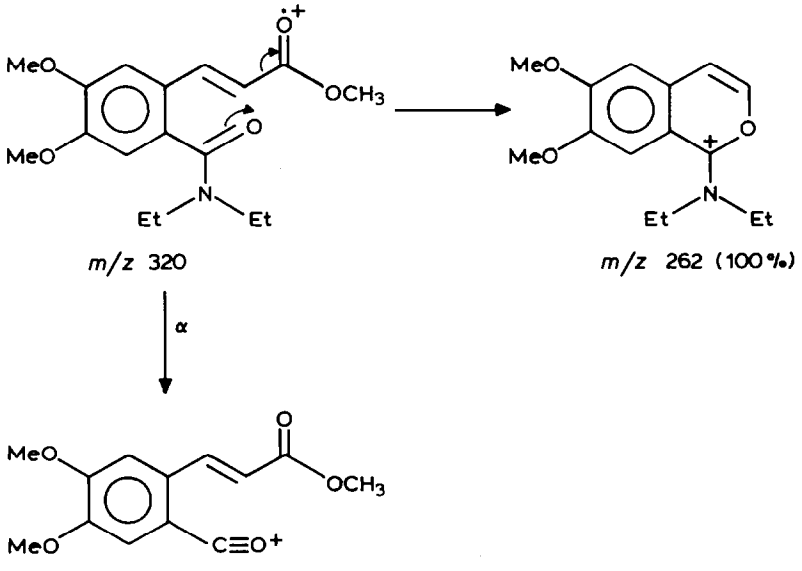
Such a loss of 73 amu from the molecular ion would be unlikely in the styrene derivative **3a**, since it would require cleavage of the conjugated π bond. Furthermore, fragmentation of the amide chain in **3a** would be expected to occur, as was observed in the parent 2-bromoamide (**2a**). Such a process, involving α-cleavage to the amide oxygen, would lead to an ion of m/z 249.



m/z 249

No ion was observed at this mass in compound **4a**. The relevant data are summarised in Table 5.

As expected, when the tertiary benzamide **2b** was subjected to the conditions of the Heck reaction, using methyl acrylate, the styrene derivative **3b** was the only product of insertion to be isolated. The mass spectrum of **3b** showed the expected ions from the fragmentation of each chain, confirmed by metastable mapping. Furthermore, no ion is observed at m/z 248 ($M - 73$) as would be expected in the phthalimidine. A number of other secondary benzamides were studied (Tables 1 and 5) and in each case the phthalimidine derivative was isolated. Yields estimated from GC analysis of the reaction mixtures were in excess of 80%, in most cases, but the



m/z 320

m/z 262 (100%)

m/z 249 (45%)

yields quoted in Table 1 refer to samples of analytical purity. In fact, the crude reaction product from **2h** was shown by GC/MS to contain (as well as **4h**) a small amount of an isomeric substance the mass spectrum of which shows no ($M - 87$) ion at m/z 278 but a small ion was observed at m/z 263 (6%). This substance is the "expected" insertion product **3h**.

TABLE 3

COUPLING CONSTANTS (Hz) FOR H_A, H_B, AND H_X IN THE PHTHALIMIDINES 4

Compound	J(AX)	J(BX)	J(AB)
4a	5.55	7.2	16.1
4c	4.1	8.9	16.25
4d	5.15	7.4	16.1
4f	6.5	5.9	16.5
4g	4.85	7.45	15.9
4h	4.2	8.0	16.0

With some benzamides, such as **2e**, it is conceivable that a six-membered ring **5**, rather than **4e** might be formed, particularly in view of the observations of Kasahara et al. [18]. However, the spectral properties of the products in these cases are so similar to those of **4a** that there is no doubt that the phthalimidines (e.g. **4e**) have been produced. In **4d**, **4f** and **4h**, the hydrogen atoms of the NCH_2 side-chain are non-equivalent and exhibit an AB quartet in the ^1H NMR spectrum (Table 2).

Since it is unlikely that the excess of triethylamine that is present in these insertion/cyclisation reactions is causing cyclisation of the first-formed styrene derivative of type **3**, it would seem that this cyclisation too is catalysed by a palladium-containing complex (cf. refs. 18 and 19). This aspect of the reaction, as well as its scope, is being investigated.

TABLE 4

^{13}C NMR SPECTRAL DATA FOR THE PHTHALIMIDINES 4 (δ in ppm)

Compound	1	11	3	4/7	5/6	8	9	10	12/13	R^2	R^4
4a				105.4	152.6						
	168.3	171.1	52.0			138.1	124.5	58.0	56.2	27.5	37.7
				104.9	150.1						
4c				105.8	153.4					136.8, 123.7, 129.3	
	167.0	171.2	51.9			138.1	124.3	57.1	56.3		37.9
				105.0	150.5					125.7	
4d				105.7	152.9					44.4	
	168.6	170.9	51.9			138.5	124.2	55.7	56.3	137.3, 127.8	38.2
				105.1	150.2					128.7, 127.6	
4f				105.6	158.1					61.3	14.1
	168.8	170.7	56.7			138.8	125.5	61.0	56.2		
				104.8	150.1					41.7, 14.1	38.2
4g				104.9	152.7					44.2	14.1
	168.6	170.4	55.7			138.6	124.1	61.0	56.2	129.8, 120.2, 111.1, 111.2	
				105.5	150.0					149.3, 148.6	37.6
4h				104.7	152.3					42.9	13.7
	168.3	170.1	56.7			138.7	123.5	62.5	55.7	100.7	
				104.6	149.5					63.0, 14.9	36.6

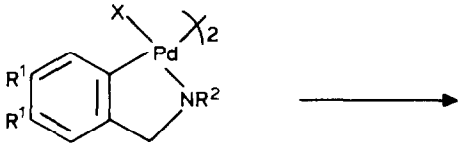
TABLE 5

IMPORTANT IONS IN MASS SPECTRA OF 2,3-DISUBSTITUTED PHTHALIMIDINES **4**; *m/z* (Relative abundance)

Compound	*M*	$M-73$ ($R^2 = CH_3$) or $M-87$ ($R^2 = C_2H_5$)	Other ions
4a	279(29)	206(100)	
4c	341(45)	268(100)	
4d	355(26)	282(43)	91(100), 264(50)
4f	365(79)	278(42)	292(100)
4g	429(43)	342(28)	151(100), 278(23)
4h	395(1)	262 [a](23)	349 [b](43), 103(100)

[a] ($M-C_2H_5OH-87$). [b] ($M-C_2H_5OH$).

O'Sullivan and Parkins [9] reported that the cyclopalladated benzylamines **6a** and **6b** react with CO in methanol at room temperature and atmospheric pressure to yield the phthalimidine derivatives **7a** and **7b**, respectively, although yields were not stated. We, too, have observed similar reactions under similar conditions using chloroform or benzene as solvent. Our results are summarised in Scheme 2 and Tables 6 and 7. We have found that only the two *N*-t-butyl derivatives gave clean-cut results. In all other cases the expected phthalimidine of type **7** was accompanied by the corresponding amino acid **8**, which was difficult to remove completely so that elemental analyses were less than satisfactory. However, the



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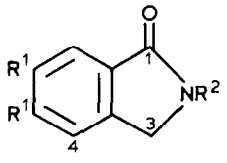
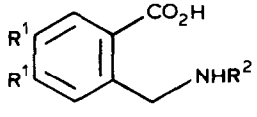


(7)

	R^1	R^2	X
a	H	H	I
b	H	Me	OAc
c	OMe	H	Br
d	OMe	Me	Br
e	OMe	t—Bu	Br
f	$2R^1 = CH_2O_2$	H	Br
g	$2R^1 = CH_2O_2$	Me	Br
h	$2R^1 = CH_2O_2$	t—Bu	Br



(8)

SCHEME 2

TABLE 6

^{1}H NMR SPECTRAL DATA FOR THE PHTHALIMIDINES 7

Compound	H(3)	H(6)	CH_2	OR	R^2	Yield (%)
7c	6.95	7.33	4.39	3.95 3.96	7.02 (br)	36.3
7d	6.91	7.31	4.29	3.94 3.94	3.18	27.7
7e	6.88	7.25	4.37	3.93 3.93	1.55	17.3
7f	6.87	7.24	4.34	6.07	6.43 (br)	41.9
7g	6.83	7.21	4.25	6.05	3.15	19.9
7h	6.80	7.15	4.33	6.02	1.54	33.9

TABLE 7

^{13}C NMR SPECTRAL DATA FOR THE PHTHALIMIDINES 7

Compound	C(1)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	OCH_3	OCH_2O	R^2
7c	172.0	45.2	105.3	149.9	153.1	105.4	124.4	137.4	56.3 56.3		
7d	168.9	51.7	105.0	149.7	152.4	105.5	125.3	134.5	56.2 56.2		29.5
7e	169.2	48.1	104.7	149.7	152.3	105.0	126.9	134.1	56.2 56.2		54.3 28.1
7g	168.4	51.8	101.8	148.2	151.1	102.9	123.5	136.3		103.5	29.5
7h	168.6	48.2	102.6	148.1	150.9	103.0	128.4	135.9		101.7	54.3 28.1

structures of the phthalimidines **7** and yields were obtained from GC/MS data. The ^{13}C NMR spectral assignments were made by using SFORD and DEPT techniques, as appropriate. Although our conditions for the insertion of carbon monoxide were less severe than those of Thompson and Heck [10], and although no loss of the *N*-substituent was noted (or expected), the method in its present form does not constitute a satisfactory synthesis of phthalimidines of this type.

Acknowledgements

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