SHORT PAPER

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A practical palladium-catalysed heteroannulation of 2-bromobenzaldehyde with alcohols and carbon monoxide leading to 3-alkoxy-3*H*-isobenzofuran-1-ones

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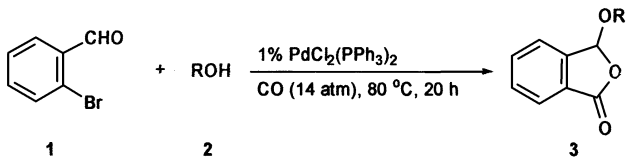
2-Bromobenzaldehyde is carbonylatively cyclised with alcohols in the presence of a catalytic amount of $PdCl_2(PPh_3)_2/PPh_3$ together with a base to afford the corresponding 3-alkoxy-3*H*-isobenzofuran-1-ones in good yields.

Keywords: alcohol, 2-bromobenzaldehyde, carbon monoxide, heteroannulation, palladium catalyst

Palladium-catalysed cyclisation reaction has been recognised as a convenient tool for the formation of many heterocyclic compounds which play an important role as a basic skeleton for the design of many pharmacologically and biologically active compounds.[1] In connection with this report, homogeneous transition metal-catalysed synthetic methods have also been attempted for the formation of 3*H*-isobenzofuran-1-one (phthalide)[2] since several phthalide-containing compounds exert a broad spectrum of physiological activities.[3] During the course of our ongoing studies on palladium-catalysed carbonylative cyclisation reactions,[4,5] we recently reported a synthetic method for the formation of 3-substituted phthalides from 2-bromobenzaldehyde and nucleophiles such as aliphatic alcohols,[6] phenols,[7] 1,3-dicarbonyl compounds,[8] sodium alkanoates[9] and carboxylic acids.[10] In the reaction with aliphatic alcohols, because the alcohols were used as solvent as well as nucleophile, the reaction using higher boiling alcohols has a drawback which is the difficulty of separation of the product from the reaction mixture. This led us to develop a practical palladium-catalysed carbonylative cyclisation of 2-bromobenzaldehyde with aliphatic alcohols in a solvent.

Table 1 shows optimisation of the conditions for the carbonylative cyclisation of 2-bromobenzaldehyde (**1**) with ethanol (**2a**) in a solvent. Generally, the reaction was performed under carbon monoxide pressure in the presence of a catalytic amount of $[PdCl_2(PPh_3)_2]$ together with base at 80°C for 20 h to give 3-ethoxy-3*H*-isobenzofuran-1-one (**3a**). Among the solvents examined for the system of $[PdCl_2(PPh_3)_2]/PPh_3/Et_3N$, THF was revealed to be the most suitable for the formation of **3a** (entries 1–4). Performing the reaction in the absence of PPh_3 gave lower yield of **3a** (entry 5). Of various organic and inorganic bases, $NaHCO_3$ was the base of choice and other bases such as DBU, pyridine and K_2CO_3 were nearly ineffective (entries 6–9).



Scheme 1

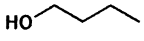
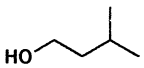
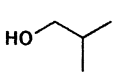
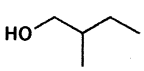
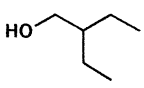
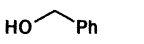
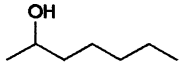
Table 1 Optimisation of conditions for the carbonylative cyclisation of **1a** with **2a**[a]

Entry	Base	Solvent	Isolated yield/%
1	Et_3N	DMF	52
2	Et_3N	MeCN	42
3	Et_3N	Toluene	70
4	Et_3N	THF	67
5[b]	Et_3N	DMF	30
6	DBU	THF	0
7	Pyridine	THF	1
8	K_2CO_3	THF	9
9	$NaHCO_3$	THF	85

[a]Reaction conditions: **1a** (1 mmol), **2a** (5 mmol), base (4 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), PPh_3 (0.04 mmol), solvent (5 ml), 80°C, 20 h. [b] In the absence of PPh_3.

Given these results, various alcohols were screened. As shown in Table 2, several primary alcohols were readily cyclised with **1** irrespective of the alkyl chain length and branch to afford the corresponding 3-alkoxy-3*H*-isobenzofuran-1-ones **3** in high yields (entries 1–5). In the reaction with

Table 2 Palladium-catalysed synthesis of **3**

Entry	Alcohol **2**		Product	Isolated yield/%
1		**2b**	**3b**	77
2		**2c**	**3c**	85
3		**2d**	**3d**	86
4		**2e**	**3e**	81
5		**2f**	**3f**	80
6		**2g**	**3g**	52
7		**2h**	**3h**	46
8		**2i**	—	0

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

2-methylbutan-1-ol (**2e**), the product **3e** was obtained as a diastereoisomeric mixture. In the case of benzyl alcohol (**2g**), a lower product yield was observed when compared with **2b**–**2f** (entry 6). The reaction also proceeded with the secondary alcohol, heptan-2-ol (**2h**) to give **3h** as diastereoisomeric mixture in 46% yield (entry 7). However, as has been observed in our recent report,[6] the carbonylative cyclisation did not occur with tertiary alcohol, 2-methylpropan-2-ol (**2i**) and the starting **1** was recovered almost completely (entry 8).

In summary, we have demonstrated that 2-bromobenzaldehyde undergo carbonylative cyclisation with alcohols in the presence of a palladium catalyst in a solvent to give 3-alkoxy-3*H*-isobenzofuran-1-ones in moderate to good yields.

Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Commercially available organic and inorganic compounds were used without further purification except for the solvent, which was distilled by known methods before use. The isolation of pure products was carried out via column chromatography (silica gel 60 GF_{254}, Merck).

General experimental procedure: A mixture of **1** (1 mmol), **2** (5 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), PPh_3 (0.04 mmol), and base (4 mmol) in anhydrous THF (5 ml) was placed in a pressure vessel. After the system was flushed and then pressurised with CO (14 atm), the reaction mixture was stirred at 80°C for 20 h. The precipitated solid was filtered off, and the filtrate was poured into brine (100 ml) and extracted with chloroform (50 ml). The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left an oil which was separated by column chromatography (hexane-ethyl acetate mixture) to give the corresponding **3**. Spectroscopic data for **3a** and **3b** are noted in our recent report.[6]

3-(3-Methylbutoxy)-3H-isobenzofuran-1-one (**3c**): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.55–1.60 (m, 2H), 1.69–1.80 (m, 1H), 3.79–3.85 (m, 1H), 3.92–3.98 (m, 1H), 6.37 (s, 1H), 7.57–7.61 (m, 2H), 7.69–7.73 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 24.9, 38.2, 68.8, 102.5, 123.4, 125.4, 127.2, 130.8, 134.4, 145.1, 168.8 (C = O).

3-Isobutoxy-3H-isobenzofuran-1-one (**3d**): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.92–2.02 (m, 1H), 3.53 (dd, *J* = 7.0 and 9.0 Hz, 1H), 3.69 (dd, *J* = 6.0 and 9.0 Hz, 1H), 6.37 (s, 1H), 7.58–7.62 (m, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2, 28.4, 76.7, 102.7, 123.4, 125.4, 127.2, 130.8, 134.4, 145.1, 168.8 (C = O).

3-(2-Methylbutoxy)-3H-isobenzofuran-1-one (**3e**): Pale yellow oil as an isomeric mixture; ^{1}H NMR ($CDCl_3$) δ 0.89–0.97 (m, 6H), 1.14–1.26 (m, 1H), 1.43–1.55 (m, 1H), 1.70–1.79 (m, 1H), 3.53-3.64 (m, 1H), 3.69–3.82 (m, 1H), 6.37 (s, 1H), 7.57–7.61 (m, 2H), 7.69–7.73 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.2 (× 2), 16.4 (16.5), 25.9 (26.0), 34.8 (34.9), 75.0 (75.2), 102.7 (102.8), 123.4 (× 2), 125.4 (× 2), 127.3 (× 2), 130.7 (× 2), 134.4 (× 2), 145.1 (× 2), 168.8 (× 2, C = O).

3-(2-Ethylbutoxy)-3H-isobenzofuran-1-one (**3f**): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 6H), 1.33–1.45 (m, 4H), 1.50–1.59 (m, 1H), 3.66 (dd, *J* = 6.0 and 9.5 Hz, 1H), 3.84 (dd, *J* = 5.5 and 9.5 Hz, 1H), 6.36 (s, 1H), 7.56–7.62 (m, 2H), 7.69–7.73 (m, 1H), 7.89 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.0, 23.2, 41.0, 72.3, 102.8, 123.4, 125.4, 127.3, 130.7, 134.3, 145.1, 168.8 (C = O).

3-Benzyloxy-3H-isobenzofuran-1-one (**3g**): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.84 (t, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 6.42 (s, 1H), 7.33–7.43 (m, 5H), 7.55–7.61 (m, 2H), 7.67–7.71 (m, 1H), 7.89 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 71.5, 101.1, 123.4, 125.4, 128.3, 128.4, 128.5, 128.6, 130.8, 134.3, 136.1, 144.9, 168.7 (C = O).

3-(1-Methylhexyloxy)-3H-isobenzofuran-1-one (**3h**): Pale yellow oil as an isomeric mixture; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3/2H), 0.93 (t, *J* = 6.9 Hz, 3/2H), 1.26–1.75 (m, 11H), 4.02–4.09 (m, 1H), 6.41 (s, 1/2H), 6.44 (s, 1/2H), 7.53–7.60 (m, 2H), 7.68–7.72 (m, 1H), 7.87 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (× 2), 19.9 (21.5), 22.5 (22.6), 25.0 (25.2), 31.7 (31.8), 36.7 (36.9), 76.9 (78.9), 101.0 (102.8), 123.3 (123.4), 125.3 (× 2), 127.2 (127.3), 130.6 (130.7), 134.2 (134.3), 145.6 (× 2), 168.8 (168.9, C = O).

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