A new route to 3-acyl-2-aminobenzofurans: palladium-catalysed cycloisomerisation of 2-(cyanomethyl)phenyl esters†

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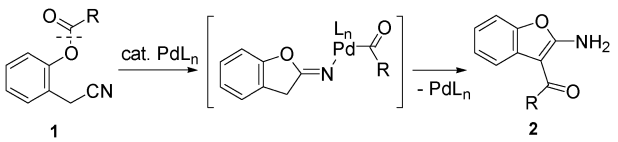
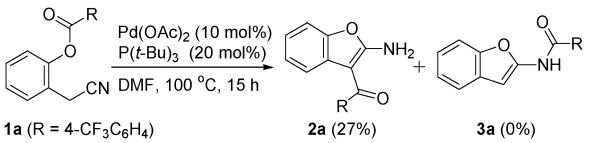
Treatment of 2-(cyanomethyl)phenyl esters with a catalytic amount of $Pd(OAc)_2$, PCy_3, and Zn afforded 3-acyl-2-aminobenzofuran derivatives in good to excellent yields, which can be used as building blocks for the synthesis of benzofuran fused heterocycles.

Transition metal-catalysed addition reactions to nitriles have received considerable attention as a potential tool for the synthesis of amines and amides.[1–4] We recently reported the copper-catalysed pyrrolinone synthesis from carbonyl-ene-nitriles and nucleophiles, in which hydration of a cyano moiety followed by dehydrative cyclisation (cycloisomerisation) produced 2-aza-2,4-cyclopentadienone as an intermediate.[5] Although several transition metal-catalysed cycloisomerisation of alkynes leading to heterocycles have been well-investigated,[6] counterparts of nitriles are limited and still remain challenging.[7] Here we report a novel palladium-catalysed cycloisomerisation of 2-(cyanomethyl)phenyl esters **1** involving cleavage of an acyl–oxygen bond and a unique intramolecular oxyacylation to a cyano moiety, which leads to the formation of 3-acyl-2-aminobenzofurans **2** (Scheme 1).



Scheme 1 Transition metal-catalysed cycloisomerisation.

Although 2-aminobenzofurans are an important class of heterocyclic compounds, they are difficult to work with because of their instability.[8] However, it is well known that substitution at the 3-position as well as *N*-acylation, remarkably increases the stability of otherwise unstable 2-aminobenzofurans.[9,10] We hypothesized that intramolecular oxyacylation of **1** *via* cleavage of the acyl–oxygen bond followed by prototropic isomerisation of a cyclic *N*-acylimino ether would give rise to a series of stable *N*-acyl-2-aminobenzofurans.[11] We first examined the reaction of 2-(cyanomethyl)phenyl 4-trifluoromethylbenzoate **1a**, which contains an acyl–oxygen bond prone to cleavage by low-valent transition metals because of activation by the electron-withdrawing CF_3 group.[12] When we carried out the reaction of **1a** in the presence of $Pd(OAc)_2$ (10 mol%) and P(*t*-Bu)$_3$ (20 mol%) in DMF at 100 °C, we isolated 3-acyl-2-aminobenzofuran (27%)[13] instead of the expected *N*-acyl-2-aminobenzofuran **3a** (eqn (1)).



(1)

This interesting result stimulated us to optimise conditions for the cycloisomerisation of **1a** (Table 1). Several phosphines including PCy_3, PCy_2Ph, and 1,1′-bis(diphenylphosphino)-ferrocene (dppf) were also effective (Table 1, entries 1–3), whereas PPh_3 was found to be ineffective for the reaction (Table 1, entry 4). Other palladium compounds including $PdCl_2$ and $Pd_2(dba)_3$ did not catalyse the reaction, even when PCy_3 was used as a ligand (data not shown in Table 1). On the other hand, the use of $Ni(cod)_2$ (10 mol%) and PCy_3 (20 mol%) produced a yield of **2a** comparable to that of the combination of $Pd(OAc)_2$ and PCy_3 (Table 1, entry 5). Since $Pd(PCy_3)_2$ might be considered the active catalyst for the present reaction, we next examined the reaction in the presence of $Pd(PCy_3)_2$. To our delight, the yield of **2a** increased to 62% yield (Table 1, entry 6). Furthermore, it was revealed that the addition of $Zn(OAc)_2$ to the $Pd(PCy_3)_2$ system was effective in facilitating the reaction to give **2a** in 96% yield (Table 1, entry 7). We also found that the reaction proceeded smoothly using the combined catalyst system of inexpensive $Pd(OAc)_2$–PCy_3–Zn to furnish **2a** in 98% yield (Table 1, entry 8).[14] The solvent DMF was found to give the best results, whereas DMSO, toluene, and dioxane decreased the yield of **2a**.

With the optimal reaction conditions ($Pd(OAc)_2$, PCy_3, and Zn powder) established, we next examined the reactions of 2-(cyanomethyl)phenyl esters **1** containing various carboxylates. The results are summarised in Table 2. All reactions were conducted in the presence of 4 Å molecular sieves (MS4A) to avoid competitive hydrolysis of **1** to 2-(cyanomethyl)phenol. Reactions of **1b–d** with the halogen at either the *ortho* or *para* position occurred smoothly and gave good yields of 3-acyl-2-aminobenzofurans **2b–d** (Table 2, entries 1–3). The cycloisomerisation described here is applicable to esters having either moderately electron-withdrawing or electron-donating substituents (Table 2, entries 4–8). Surprisingly, 2-(cyanomethyl)phenyl acetate **1j** also afforded

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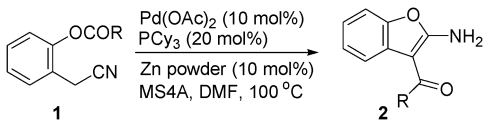
Table 1 Optimization of cycloisomerisation of **1a**[a]

Entry	[M]–ligand–additive	Conversion (%)	Yield (%)[b]
1	$Pd(OAc)_2$–PCy_3	54	36
2	$Pd(OAc)_2$–PCy_2Ph	53	31
3[c]	$Pd(OAc)_2$–dppf	78	32
4	$Pd(OAc)_2$–PPh_3	79	0
5	$Ni(cod)_2$–PCy_3	68	32
6	$Pd(PCy_3)_2$	68	62
7[d]	$Pd(PCy_3)_2$–$Zn(OAc)_2$	100	96
8[e]	$Pd(OAc)_2$–PCy_3–Zn	100	98

[a] Reaction conditions: **1a** (0.40 mmol), [M] (0.040 mmol), ligand (0.080 mmol) in DMF (2.0 mL) was stirred at 100 °C for 15 h. [b] Isolated yields. [c] Dppf (10 mol%) was used. [d] $Zn(OAc)_2$ (0.040 mmol) was used. [e] Zinc powder (0.040 mmol) was used.

Table 2 Palladium-catalysed cycloisomerisation of 2-(cyanomethyl)-phenyl esters **1**[a]



1 2

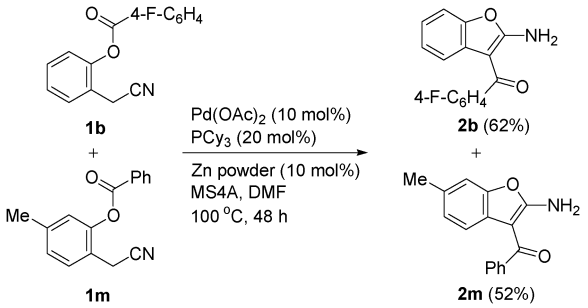
Entry	R		Time/h	Product	Yield (%)[b]
1	$4\text{-}FC_6H_4$	**1b**	24	**2b**	74
2	$4\text{-}ClC_6H_4$	**1c**	24	**2c**	79
3	$2\text{-}ClC_6H_4$	**1d**	24	**2d**	91
4	2-Naph	**1e**	24	**2e**	89
5	Ph	**1f**	72	**2f**	68
6	$4\text{-}MeC_6H_4$	**1g**	72	**2g**	71
7	$4\text{-}MeOC_6H_4$	**1h**	72	**2h**	64
8	$4\text{-}Me_2NC_6H_4$	**1i**	96	**2i**	68
9	Me	**1j**	72	**2j**	57
10	H	**1k**	60	**2k**	50
11	OEt	**1l**	24	**2l**	68

[a] Reaction conditions: **1** (0.40 mmol), $Pd(OAc)_2$ (0.040 mmol), PCy_3 (0.080 mmol), Zn powder (0.040 mmol) and MS4A (40 mg) in DMF (2.0 mL) at 100 °C. [b] Isolated yields.

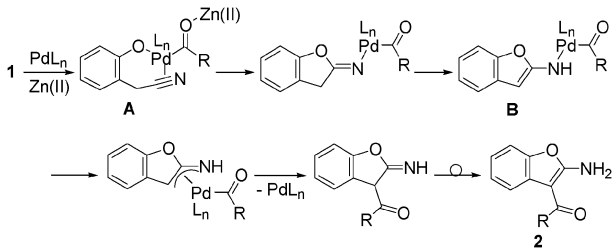
3-acetyl-2-aminobenzofuran **2j** in 57% yield (Table 2, entry 9). Furthermore, the substrate scope could be expanded to formate **1k** and carbonate **1l**, giving 2-amino-3-formylbenzofuran **2k** and 2-amino-3-ethoxycarbonylbenzofuran **2l** in 50% and 68% yields, respectively (Table 2, entries 10 and 11).

To gain an insight into the reaction mechanism, a crossover experiment was carried out (Scheme 2). Palladium-catalysed cycloisomerisation of a mixture of equimolar amounts of esters **1b** and **1m** yielded only two types of 3-acyl-2-aminobenzofurans, **2b** and **2m** without any crossover products. This result clearly shows that the present cycloisomerisation reaction proceeds in an intramolecular fashion.

Although the details of the process remains unknown, we propose the following mechanism for the reaction involving oxidative cleavage of an acyl–oxygen bond with the low-valent palladium species (Scheme 3).[12,15] The oxidative cleavage of an acyl–oxygen bond with transition metals is known to be difficult to achieve, except in the case of esters activated by electron-withdrawing groups[12] and esters having 2-pyridylmethyl as a directing group.[16] In the present reaction



Scheme 2 Crossover experiment.



Scheme 3 Plausible reaction mechanism.

$Zn(OAc)_2$, which is generated from the reaction of $Pd(OAc)_2$ with zinc, might accelerate the oxidative cleavage of an acyl–oxygen bond forming an intermediate **A** by coordination to the carbonyl group.[17] In the next step, oxypalladation of a cyano moiety followed by prototropic isomerisation gives the intermediate **B**. Subsequent σ–π isomerisation of an azaallyl–palladium, and reductive elimination at the 3-position of the benzofuran, yields 3-acyl-2-aminobenzofuran **2**, and regenerates the catalyst.[18,19]

Since 3-acyl-2-aminobenzofurans have both an amino and a carbonyl group, they are considered key building blocks for the synthesis of benzofuran fused heterocycles. Elbfluorene **7**, which is a CDK (cyclin-dependent-kinase) inhibitor is a logical target for the application of 3-acyl-2-aminobenzofuran.[20] A synthesis of elbfluorene **8** has been accomplished *via* 6 steps involving the palladium-catalysed cycloisomerisation of **1n** and the subsequent annulation (Scheme 4).

In conclusion, we have developed a unique palladium-catalysed cycloisomerisation of 2-(cyanomethyl)phenyl esters. The reaction provides a new route to 3-acyl-2-aminobenzofurans, which are rather inaccessible substituted heterocyclic structures. Furthermore, 3-acyl-2-aminobenzofurans are applicable to the synthesis of biologically active nitrogen-containing heterocycles as demonstrated by the synthesis of elbfluorene. Further mechanistic investigations and studies on synthetic applications are now in progress in our laboratory.

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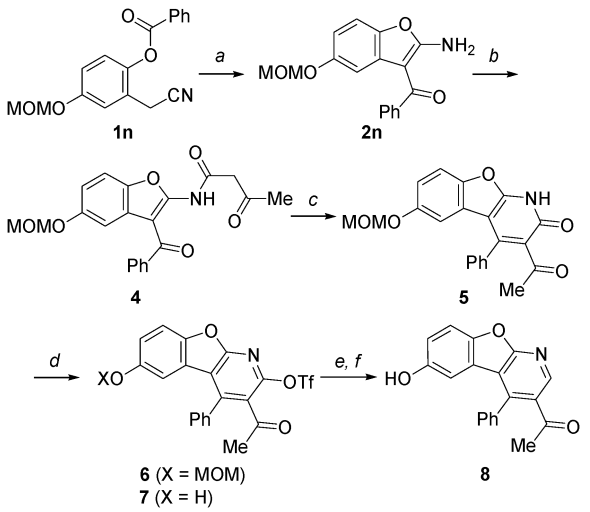

Scheme 4 Reagents and conditions: (a) $Pd(OAc)_2$, PCy_3, Zn powder, MS4A, DMF, 100 °C, 9 h, 78%; (b) diketene, TMSCl, MeCN, 50 °C, 18 h; (c) NaOMe, MeOH, rt, 8 h; (d) Tf_2O, pyridine, CH_2Cl_2, −78 °C ∼ rt, 2 h, 56% (3 steps); (e) HCl, THF, 50 °C, 8 h, 78%; (f) Et_3SiH, $Pd(OAc)_2$, dppf, DMF, 70 °C, 3 h, 96%. MOM = methoxymethyl.

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