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Synthesis of 3-substituted isoindolin-1-ones via a palladium-catalysed 3-component carbonylation/amination/Michael addition process

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Abstract—A novel palladium-catalysed three component cascade process is described involving carbonylation of an aryl iodide to generate an acyl palladium species which is intercepted by a primary aliphatic/aromatic amine, amide or sulfonamide followed by intramolecular Michael addition to afford 3-substituted isoindolin-1-ones in good yield.
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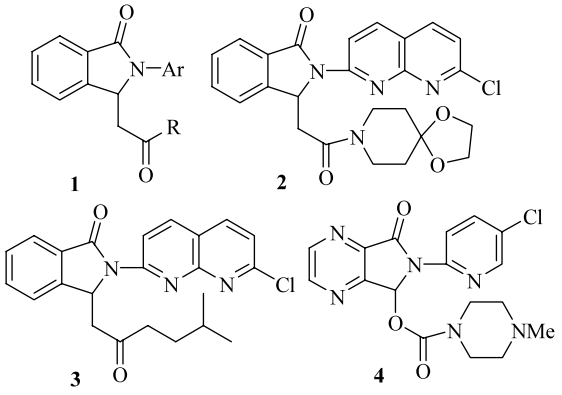
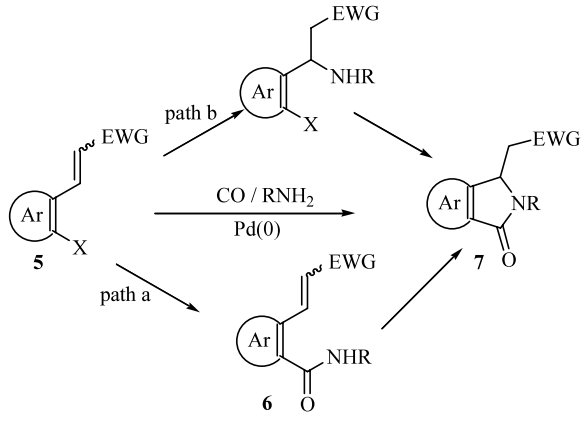
Substituted isoindolinones of general structure **1** possess anxiolytic activity and are of interest as sedatives, hypnotics and muscle relaxants.[1] Typical examples are the anxiolytics pazinaclone **2**, pagoclone **3** (Aventis/Pfizer–phase III clinical trials),[2] and the anxiolytic/anticonvulsant zopiclone **4**.[3] The isoindolone moiety also features in anti-cancer drug candidates including protein kinase inhibitors.

We have demonstrated that carbon monoxide and allene are powerful relay switches in the palladium-catalysed cyclisation–anion capture cascades.[4] As part of our ongoing interest in designing palladium-catalysed carbonylation processes in a tactical combination with core reactions, we explored combinations with Michael addition processes as the key step to synthesise isoindolinone derivatives (Scheme 1).

Compounds of type **5** react with carbon monoxide (1 atm) and a primary amine in the presence of palladium(0) to afford 3-substituted isoindolin-1-ones via path **a** or path **b**. In path **a** carbon monoxide insertion is followed by amination to give the amide **6**, which





Scheme 1.

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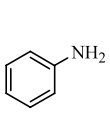
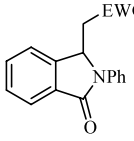
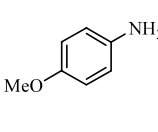
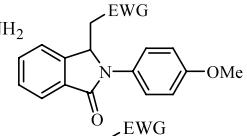
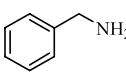
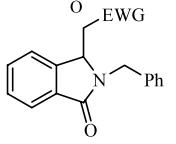
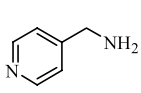
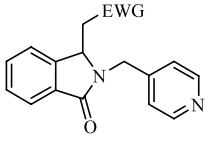
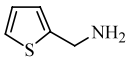
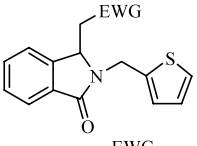
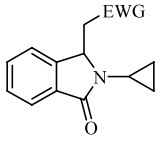
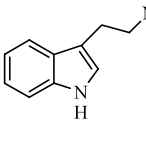
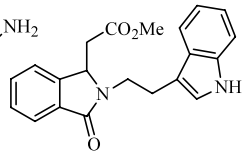
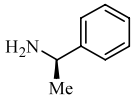
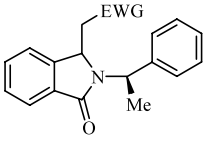
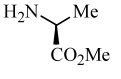
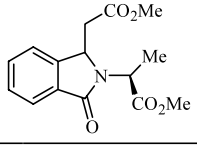
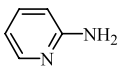
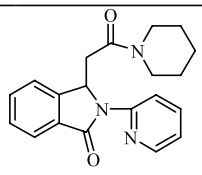
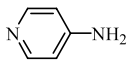
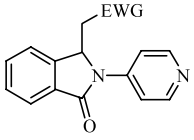
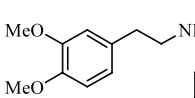
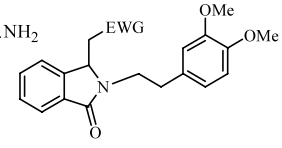
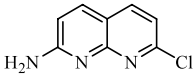
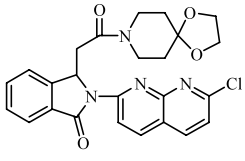
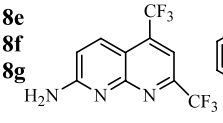
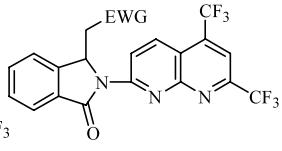
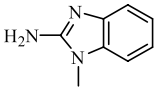
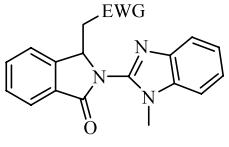
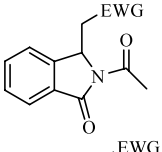
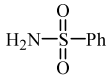
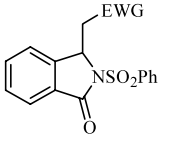
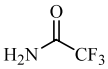
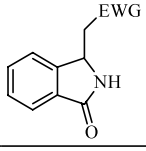
Table 1. Three component carbonylation–amination-Michael addition cascades[a]

Entry	Aryl iodide	Nucleophile	Product	Yield (%)[b]
1	**8a** **8b**			**9a** 75 **9b** 65
2	**8a** **8b**			**10a** 90 **10b** 79[c]
3	**8a** **8b** **8c** **8d**			**11a** 91 **11b** 69 **11c** 61 **11d** 70
4	**8a** **8b**			**12a** 95 **12b** 88
5	**8a** **8b** **8c** **8d**			**13a** 87 **13b** 77 **13c** 55 **13d** 55
6	**8a** **8b**			**14a** 79 **14b** 52
7	**8a**			**15** 69
8	**8a** **8b**			**16a** 70 (1:1) **16b** 77[c] (2:3)
9	**8a**			**17** 63[c] (1:1)

a. All reactions were carried out in toluene at 90 °C for 24 h and employed 1 mol of aryl iodide/Michael acceptor, carbon monoxide (1atm), 10 mol% $Pd(OAc)_2$ 20 mol% PPh_3, 2 mol eq Cs_2CO_3 and 1.2 mol eq amine. b. Isolated yields c. Reaction time 48 h

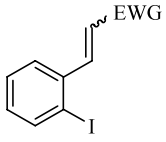
undergoes intramolecular Michael addition to afford substituted isoindolin-1-ones **7**. In path **b** an intermolecular Michael addition occurs first. We selected **8a–j** as the prototypical dual aryl iodide/Michael acceptors to evaluate this novel 3-component cascade. Recently we have reported a similar process but using allene as a relay switch, in place of CO, to synthesise carbo- and hetero-cycles.[5] Thus **8a–d** (1 mmol) react

Table 2. Three component carbonylation cascade with α,β-unsaturated amide Michael acceptors[a,b]

Entry	Aryl iodide	Nucleophile	Product	Yield (%)[c]
1	**8e**			**18** 86[a]
2	**8e** **8f** **8h** **8i** **8j**			**19e** 92[a] **19f** 99[a] **19h** 88[a] **19i** 58[a] **19j** 89[a]
3	**8e** **8g**			**20e** 85[a] **20g** 96[a]
4	**8f**			**2** 64[b]
5	**8e** **8f** **8g**			**21e** 86[b] **21f** 90[b] **21g** 87[b]
6	**8g** **8i**			**22g** 75[b] **22i** 75[b]
7	**8e** **8f** **8h**			**23e** 62[b] **23g** 52[b] **23h** 43[b]
8	**8e** **8h**			**24e** 56[b] **24h** 59[b]
9	**8e** **8f**			**25e** 60[b] **25f** 62[b]

a. Reactions were carried out in toluene at 90 °C for 18 h and employed 1 mol of aryl iodide/Michael acceptor, carbon monoxide (1atm), 2.5 mol% $Pd_2(dba)_3$, 20 mol% TFP, 2 mol eq Cs_2CO_3 and 1.2 mol eq amine. b. Reactions were carried out in dioxane at 110 °C and employed 2 mol% $Pd(PPh_3)Cl_2$ and 12 mol% TFP, 2 mol eq Cs_2CO_3 and 1.2 mol eq. amine c. Isolated yields.

with carbon monoxide (1 atm), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 mol equiv.) and an aromatic/hetero-aromatic or aliphatic amine (1.2 mol equiv.) in toluene at 90°C for 24 h to afford heterocycles **9**–**15** in good yield (Table 1, entries 1–7). Next, we briefly studied the diastereoselectivity of the Michael addition reaction in the presence of a chiral amine (Table 1, entries 8 and 9). (*R*)-(+)-α-Methylbenxylamine afforded **16a** and **16b** as 1:1 and 2:3 diastereomeric mixtures whilst *S*-alanine methyl ester afforded **17** as a 1:1 diastereomeric mixture.



8

a. EWG = CO_2Me (*E*:*Z*=5:1 b. EWG = CN *Z* only)

c. EWG = COMe (*E* only) d. EWG = COPh (*E* only)

e. EWG = CO—N (*E* only)

f. EWG = CO—N (*E* only)

g. EWG = CO—N (*E* only)

h. EWG = CO—N NMe (*E* only)

i. EWG = CO—N N— (*E* only)

j. EWG = CO—N(H)— (*E* only)

A further interesting high yielding cascade of particular biological importance is revealed when heterocyclic amides **8e**–**j** were employed as the electron withdrawing group on the Michael acceptor. In these cases, the catalyst system comprised 2.5 mol% Pd_2dba_3/10 mol% tris (2-furyl) phosphine/K_2CO_3 (2 mol equiv.) in toluene and the products **18**–**20** are obtained in excellent yield (Table 2, entries 1–3). When electron withdrawing bicyclic aromatic amines were employed as nucleophiles, a modified catalyst system consisting of $Pd(PPh_3)_2Cl_2$ 10 mol%, TFP 12 mol% and Cs_2CO_3 (2 mol equiv.) in toluene at 110°C was used (Table 2, entries 4–6). Pazinaclone **2** was successfully synthesised in 64% yield (unoptimised) (Table 2, entry 4). Amides and sulfonamides were also successfully used as nucleophiles in the above cascades (Table 2, entries 7 and 8).

When trifluoroacetamide was employed as a nucleophile, hydrolysis occurred furnishing NH amides **25e** and **25f** in good yield (entry 9). This opens up further synthetic opportunities.

We have briefly probed the mechanism of the reaction and conclude that it is more likely to proceed via path **a** than path **b**. A control experiment in which carbon monoxide was omitted as the reagent and benzylamine used as a nucleophile was carried out but no Michael adduct, resulting from the reaction of **8a** with benzylmine, was detected under the standard reaction conditions.

In conclusion, we have demonstrated a novel three component palladium-catalysed carbonylation/amination/Michael addition cascade for the synthesis of 3-substituted isolindolin-1-ones. Further work is in hand on this and related cascades.

Acknowledgements

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