Pergamon

Tetrahedron Letters 43 (2002) 2601–2603

TETRAHEDRON
LETTERS

# Synthesis of *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolin-1-ones via a palladium-catalysed three-component process

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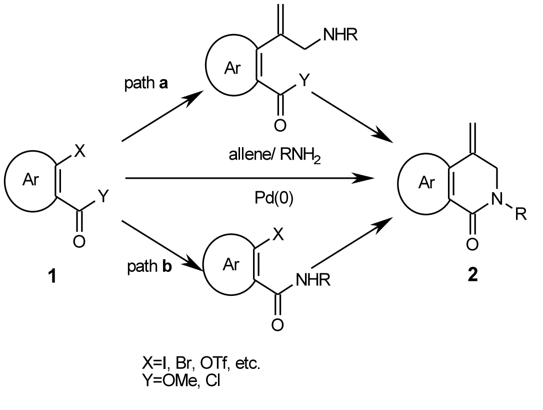
Received 25 September 2001; revised 4 February 2002; accepted 12 February 2002

**Abstract**—A novel palladium-catalysed three-component cascade process involving 2-iodobenzoyl chloride or methyl 2-iodobenzoate, allene and primary aliphatic or aromatic amines furnishes *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolin-1-ones in good yield. © 2002 Elsevier Science Ltd. All rights reserved.

Allenes are versatile building blocks in palladium-catalysed processes but are still under utilised in organic synthesis.[1] They function as powerful relay-switches in palladium-catalysed cyclisation-anion capture cascades.[2] Reactions of aryl/vinyl palladium(II) intermediates with allene lead to the formation of (π-allyl)palladium species able to undergo a wide range of transformations, including attack by nucleophiles,[3] electrophiles[4] or transmetallation.[5] In the context of heterocycle synthesis allenes offer expeditious routes to a wide range of oxygen and nitrogen heterocycles.[1] A further feature of incorporation of allenes into heterocycle synthesis is their ability to provide unusual substituents and substitution patterns. Particularly useful is the ability to engineer *exo*-methylene and 1,1-disubstituted *exo*-methylene moieties from allenes.[6] Recently, we have developed several three-component syntheses of chroman-4-ones and quinolin-4-ones.[7–9] As part of our ongoing interest in designing heterocyclic syntheses involving palladium-catalysed multicomponent processes utilising allenes,[7] we explored the following process (Scheme 1), with both esters (**1**, Y = OMe) and acyl chlorides (**1**, Y = Cl).



**Scheme 1.**

2-Iodoesters (**1**, X = I, Y = OMe) would be expected to react with allene and a primary amine via path **a** to afford **2**, whereas 2-iodo acyl chlorides (**1**, X = I, Y = Cl) would be expected to react with allene and a primary amine via path **b** to give **2**. In this communication we report examples of both path **a** and path **b** processes. We selected methyl 2-iodobenzoate as the prototypical ester component. Methyl 2-iodobenzoate (1 mmol) reacted with allene (1 bar), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), K$_2$CO$_3$ or Cs$_2$CO$_3$ (2 mol equiv.) and an aliphatic primary amine (1.2 mol equiv.) in toluene (10 ml) at 100°C for 24 h to afford **3**–**6** in good yield (Table 1).

Next, we briefly studied the use of chiral primary amines in the cascades (Table 1, entries 5–8). Thus, using (*R*)-(+)-α-methylbenzylamine, (*S*)-(−)-2-amino-1-methoxypropane, *S*-alanine methyl ester and *S*-phenylalanine methyl ester, afforded **7**–**10** in good yields

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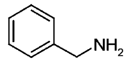
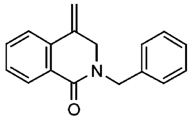
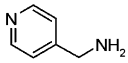
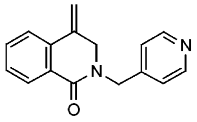
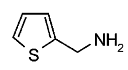
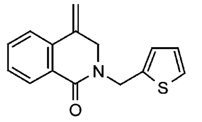
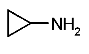
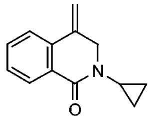
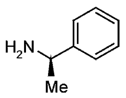
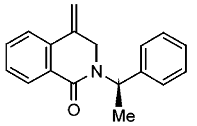
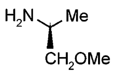
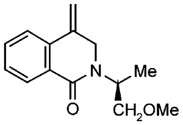
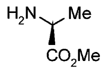
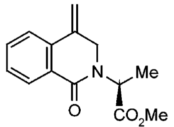
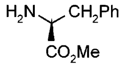
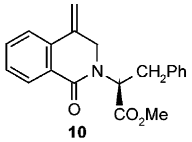
PII: S0040-4039(02)00329-5

**Table 1.** Three-component allenylation–amination cascades[a]

| Entry | Nucleophile | Product | Yield (%)[b] |
|---|---|---|---|
| **1** |  | <br>**3** | 75[c,e] |
| **2** |  | <br>**4** | 98[c,e] |
| **3** |  | <br>**5** | 83[c,e] |
| **4** |  | <br>**6** | 79[c,e] |
| **5** |  | <br>**7** | 95[d,e] |
| **6** |  | <br>**8** | 76[d,e] |
| **7** |  | <br>**9** | 81[d,f] |
| **8** |  | <br>**10** | 70[d,f] |

[a] All reactions were carried out in toluene at 100°C for 24 h and employed 1 mmol methyl 2-iodobenzoate, 10 mol% Pd(OAc)$_2$, 20 mol% PPh$_3$, 2 mol equiv. K$_2$CO$_3$ or Cs$_2$CO$_3$ and 1.2 or 2 mol equiv. amine.

[b] Isolated yields.

[c] Cs$_2$CO$_3$ as base.

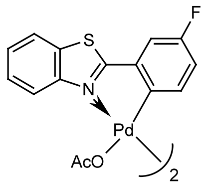
[d] K$_2$CO$_3$ as base.

[e] 1.2 mol equiv. amine.

[f] 2 mol equiv. amine.

(Table 1, entries 5–8). In no cases was any racemisation detected.

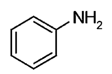
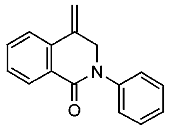
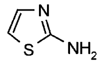
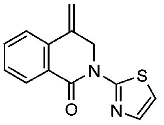
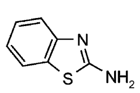
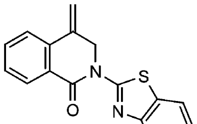
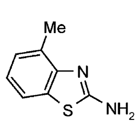
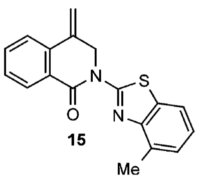
The use of aromatic and heteroaromatic amines in the above cascades afforded lower yields of *N*-aryl 4-methylene-3,4-dihydro-1(2*H*)-isoquinolinones. We therefore explored the path **b** process for these amines with 2-iodobenzoyl chloride. Thus, 2-iodobenzoyl chloride (1.4 mmol) reacted with allene (1 bar), catalyst **11** (5 mol%),[10] an aromatic or heteroaromatic amine (1 mmol), Cs$_2$CO$_3$ (2 mol equiv.) and 4 Å molecular sieves (3 g) in toluene (10 ml) at 100°C for 24 h to afford **12–15** in 53–70% yield (Table 2).



**11**

We also confirmed that the mechanism of the above reaction employing methyl 2-iodobenzoate follows path **a**, whereas 2-iodobenzoyl chloride follows path **b**. Thus, when the reaction of 2-iodobenzoyl chloride with 2-aminothiazole (Table 2, entry 2) was left for 24 h, a 1:1 mixture of **13** and **16** was obtained. Increasing the reaction time to 48 h resulted in the sole formation of **13**.

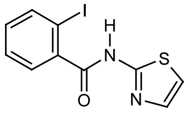
**Table 2.** Three-component allenylation–amination cascades[a]

| Entry | Nucleophile | Product | Yield (%)[b] |
|---|---|---|---|
| **1** |  | <br>**12** | 55 |
| **2** |  | <br>**13** | 63[c] |
| **3** |  | <br>**14** | 70 |
| **4** |  | <br>**15** | 53 |

[a] All reactions were carried out in toluene at 100°C for 24 h and employed 1.4 mmol 2-iodobenzoyl chloride, 5 mol% catalyst **11**, 2 mol equiv. Cs$_2$CO$_3$ and 1.2 mol equiv. amine.

[b] Isolated yields.

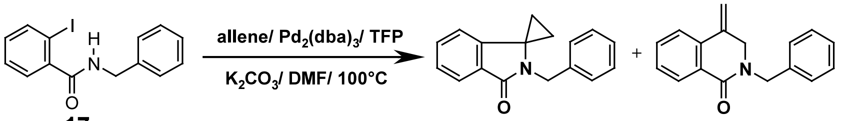
[c] Reaction time 48 h.



**16**

Evidence for the reaction of methyl 2-iodobenzoate proceeding via path **a**, rather than path **b**, was gained from the reaction of 2-iodobenzamide **17** in the presence of allene (1 bar), $Pd_2(dba)_3$ (5 mol%), tri-2-furylphosphine (TFP) (10 mol%) and $K_2CO_3$ (2 mol equiv.) in DMF at 100°C for 24 h, which afforded a 1:1 mixture of **18** and **3**.[11]

In our cascade (Table 1, entry 1) we did not observe **18**. Moreover, a control experiment reacting methyl 2-iodobenzoate (1 mmol) and benzylamine (1 mmol) in toluene (10 ml) at 100°C for 24 h failed to give amide **17**.



**17** **18** **3**

In conclusion, we have developed two complementary three-component cascades for the synthesis of *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolinones. Further work is in hand incorporating substituted allenes into this cascade.

## Acknowledgements

We thank Leeds University and the Thailand Research Fund (TRF) of the Royal Golden Jubilee project for support.

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