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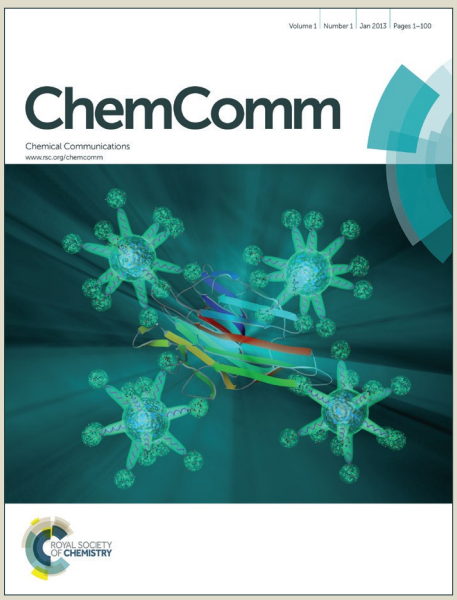

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ARTICLE TYPE

A Facile Palladium Catalysed 3-Component Cascade Route to Functionalised Isoquinolinones and Isoquinolines

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Palladium catalysed three component cascade process, involving coupling of 2-iodobenzoates, -benzaldehydes, or acetophenones with substituted allenes and ammonium tartrate as an ammonium surrogate, provides a novel and facile route to substituted functionalised isoquinolinones and isoquinolines in good yields.

Isoquinolinone and isoquinoline derivatives are important constituents of a diverse range of molecules of biological and pharmaceutical relevance as well as a common structural component within many alkaloids.[1,2,3] However, little attention has been given to approaches to these systems which utilise metal-catalysed aryl-allene couplings, despite the obvious potential of this route to produce such systems with high degrees of chemo- and regioselectivity. Nonetheless, the potential of this approach has been underlined previously. Thus, Larock reported that annulation of a substituted allene with N-tosyl-2-iodobenzylamine under Pd(II) catalysis afforded isoquinolines as a mixture of three regio- and stereo-isomers.[4] Additionally, 2-iodobenzaldehyde imines have also been used with Pd(0) catalysis to annulate substituted allenes giving isoquinoline derivatives.[5] Ni(0)/chiral phosphine ligand mediated regio- and enantioselective synthesis of isoquinoline-1(2H)-one derivatives has been reported via denitrogenation or decarbonylation of N-aryl-1,2,3-benzotriazin-4(3H)-ones or N-substituted phthalimide, respectively, followed by intermolecular annulation with substituted allenes.[6] Recently, Glorius et al., employed Rh(III) to catalyse C-H activation of N-(pivaloyloxy)benzamide involving intermolecular annulation with substituted allenes to furnish isoquinoline-1(2H)-ones.[7]

As part of our program of research into the development and application of palladium catalysed allene insertion cascades, we have previously reported a number of examples of three-component cascades for the synthesis of *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolinones. A feature of these reactions is that, following an initial Pd- mediated intramolecular allene insertion, both intra- and intermolecular nucleophilic addition then occurs to give tetra-fused ring systems containing an isoquinolinone ring.[8, 9a] These include, following the initial Pd catalysed intramolecular allene insertion, intermolecular nucleophilic addition involving N-allenyl-2-iodobenzamide,[9b,c] and nitrogen-tethered 1,6-enynes[9d] respectively. Additionally, we have also reported two types of cascade reactions that can furnish isoquinolines; (i) intermolecular allene insertion into the C-I bond of an aryl iodide linked *N*-nucleophile followed by intramolecular *N*-addition to the generated π-allyl,[10] and (ii) intermolecular allene insertion to an aryl iodide carrying a dipolarophile/Michael acceptor followed by intermolecular *N*-addition of an azide/amine and finally intramolecular 1,3-dipolar cycloaddition/Michael addition.[11]

In the present study, we report a new approach utilising our "ammonium surrogate" technology[12] as a novel ammonia source to furnish substituted functionalised isoquinolinone and isoquinoline derivatives. Thus, methyl 2-iodobenzoate derivatives **1** were reacted with a range of substituted allenes **2** in the presence of ammonium tartrate (6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (`10 mol%), and K_2CO_3 (3 equiv.), to afford isoquinolinones **4** *via* intramolecular cyclisation of the intermediate **3** in 51-78% yield (Table 1). Z-configuration of the exocyclic double bonds were established using NOE data (see the Experimental Section) and in the absence of ammonium tartrate, no reaction occurred, and only starting materials were observed. This appears to be consistent with a mechanism involving the addition of ammonia to the π-allyl intermediate forming amine **3** which subsequently cyclises to give **4**. Thus, the cyclisation step in **3**→**4** is faster than further allylation of the allyl-NH_2 group. In the case of methyl 5-bromo-2-iodobenzoate (**1**, R^1 = 5-Br), the reaction is chemoselective for oxidative addition at the C-I bond leaving the

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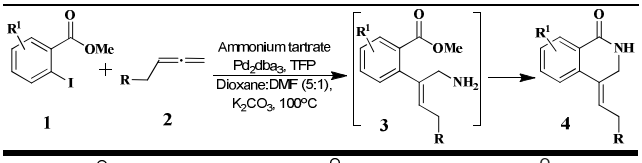
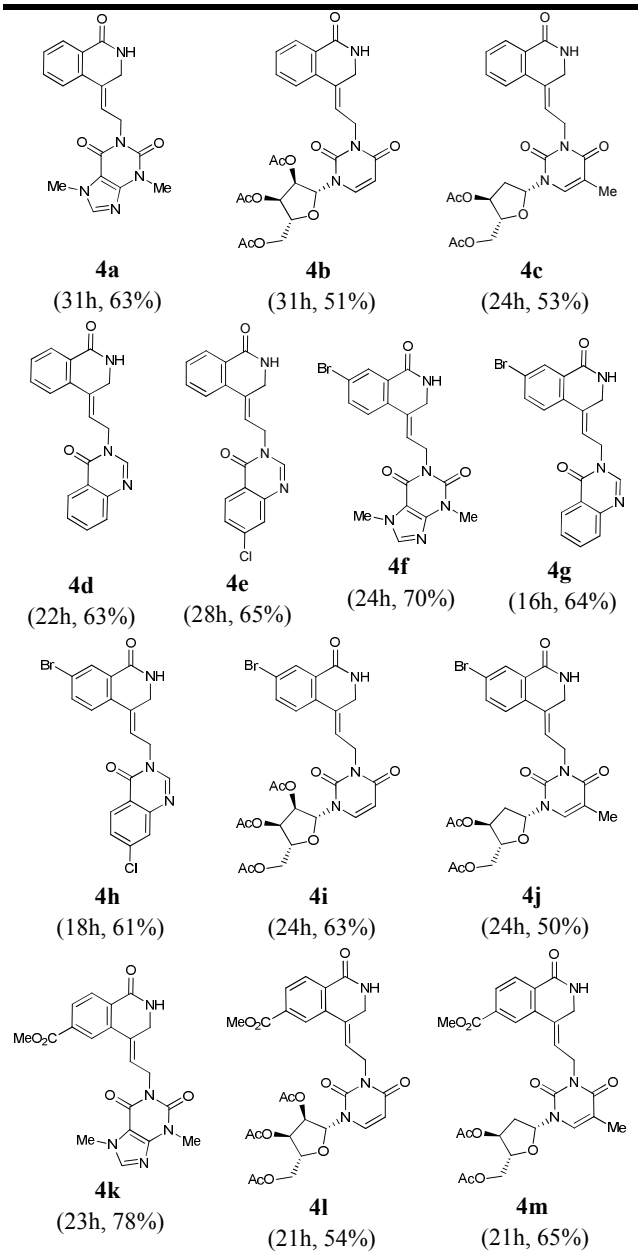
C-Br bond intact. It is also noteworthy that the ester moieties in **4k-m** were unchanged under the reaction conditions.

Table 1. Pd(0) catalysed annulation of allenes with methyl 2-iodobenzoates.



1 2 3 4



4a (31h, 63%) **4b** (31h, 51%) **4c** (24h, 53%)

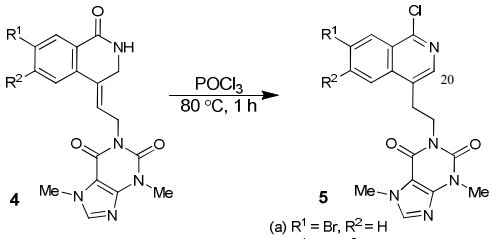
4d (22h, 63%) **4e** (28h, 65%) **4f** (24h, 70%) **4g** (16h, 64%)

4h (18h, 61%) **4i** (24h, 63%) **4j** (24h, 50%)

4k (23h, 78%) **4l** (21h, 54%) **4m** (21h, 65%)

Reactions carried out at 100 ºC in 1,4-dioxane/DMF (5:1) for 16-31h and employed substituted allene **2** (1 equiv.), **1** (1.2 equiv.), ammonium tartrate (6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (`10 mol%), and K_2CO_3 (3 equiv.). Figures in brackets indicate reaction time and isolated yields.

In order to briefly explore the potential of adducts **4** for further synthetic manipulation, compounds **4f** and **4k**, selected as representative examples, were converted into the corresponding 1-chloroisoquinolines **5a** and **5b** in the presence of $POCl_3$, (Scheme 1). The assignment of the structures of the chlorination products to chloropyridines **5a** and **5b** followed from analysis of the ^{1}H-NMR data for these compounds. This revealed the absence of allyl signals (typically a triplet at ~6-6.5 ppm and doublet at ~4.5-5 ppm respectively), and instead, comprised an AA′BB′ nmr pattern for the two methylene groups at 3-3.5 and 4-4.5 ppm respectively, consistent with the assigned structures. (see Supporting Information).



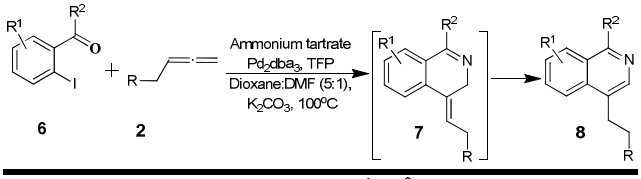
4 5

(a) R^1 = Br, R^2 = H
(b) R^1 = H, R^2 = CO_2Me

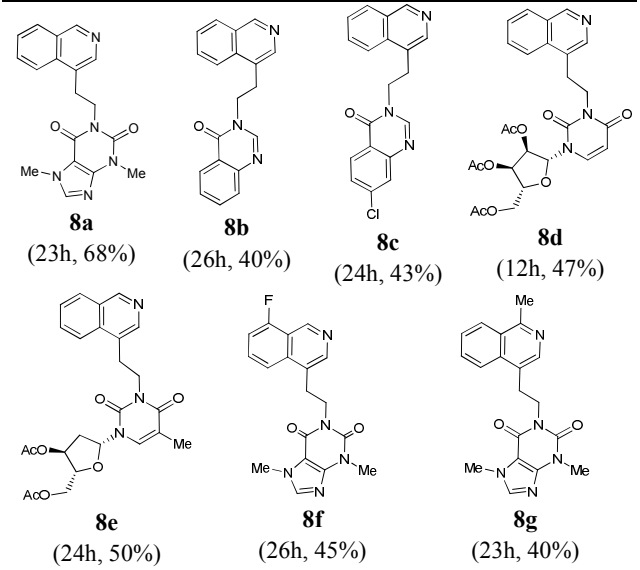
Scheme 1. Conversion of isoquinolinone to isoquinoline.

To further probe the scope of this process, the reaction of 2-iodobenzaldehydes/2′-iodoacetophenone **6** with substituted allenes **2** was explored. This reaction presumably goes via intermediate **7** which undergoes a 1,3-hydrogen rearrangement generating isoquinolines **8**, Table 2. Analogously to isoquinoline **5a** and **5b**, ^{1}H-NMR data (see Supporting Information) showed no indication of allyl signals but instead included an AA′BB′ pattern for the two methylene groups present in **8**. The somewhat low yields of products from this reaction may reflect the thermal instability of the substrates or the products. This hypothesis appears to be supported by the isolation of theobromine (in the case of **8a,f** and **g),** 2',3',5'-tri-*O*-acetyluridine (in case of **8d**), 3',5'-tri-*O*-acetylthymidine (in case of **8e**), quinazolin-4-one (in case of **8b**) and chloroquinazolin-4-one (in case of **8c**) as by-products. It is noteworthy that thermal degradation of products was not observed in the preparation of isoquinolinones **4a-m**.

Table 2. Pd(0) catalysed preparation of isoquinolines **8**.



6 2 7 8



8a (23h, 68%) **8b** (26h, 40%) **8c** (24h, 43%) **8d** (12h, 47%)

8e (24h, 50%) **8f** (26h, 45%) **8g** (23h, 40%)

Reaction carried out at 100 ºC in 1,4-dioxane/DMF (5:1) for 12-26h and employed substituted allene **2** (1 equiv.), **6** (1.2 equiv.), ammonium tartrate (6 equiv.), $Pd_2(dba)_3$ (2.5 mol%), TFP (10 mol%), and K_2CO_3 (2-3 equiv.).

In summary, a novel and powerful cascade approach has been applied to the synthesis of substituted functionalised isoquinolinone and isoquinoline derivatives *via* 3-component palladium catalysed cascade chemistry. The utility of ammonium tartrate as a novel ammonia source is underlined in this simple one-pot cascade protocol.

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