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A new (3+3) annulation route to isoquinoline-3-carboxylates†

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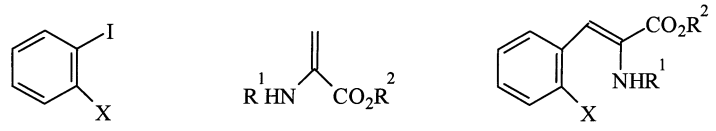
Abstract—A new synthesis of isoquinoline-3-carboxylates based on the palladium(0)-catalysed Heck-type arylation of 2-amidoacrylates with the appropriate 2-substituted iodobenzene is reported.

The isoquinoline ring system is found in many alkaloids[1] and for this and other reasons the synthesis of isoquinoline derivatives has received considerable attention. Most of the classical methods[2] employ comparatively harsh conditions, and therefore have obvious limitations. A few milder approaches have also been reported.[3] In recent years, a number of heterocyclic ring systems have been conveniently prepared[4] using palladium(0)-catalysed reactions, and annulation strategies based on such catalysis have recently been reported for the synthesis of isoquinolines.[5] We,[6] and others,[7] have demonstrated that Pd(0)-catalysed olefination of haloaromatics with 2-amidoacrylates gives the corresponding 2-amidocinnamates with very high stereoselectivity. In this communication, we wish to disclose how this selectivity can be exploited for a cyclo-functionalisation leading to a new synthesis of isoquinoline-3-carboxylates.

We argued that a Heck-type olefination[8] of a 2-substituted iodoarene of type **1** (Fig. 1) with the 2-amidoacrylate **2** should give a substrate **3** containing an



1 **2** **3**

X	R^1	R^2
1a,3a ; CO_2Me	**2a,3a-b,3d** ; $COCH_3$	**2a,3a-b,3d** ; Me
1b ; CHO	**2b,3c,3e** ; CO_2CMe_3	**2b,3c,3e** ; CH_2Ph
1c,3d-e ; 		
3b,3c ; CH_2OH		

Figure 1.

Keywords: Heck reaction; 2-amidoacrylates; isoquinoline-3-carboxylates.

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electrophilic and a nucleophilic partner for a C–N bond forming ring closing reaction. The known[6,7] *Z*-selectivity of the reaction delivers these complementary functionalities in the proximity necessary for a facile cyclisation. This proved to be a realistic proposition when methyl 2-iodobenzoate was reacted with methyl 2-acetamidoacrylate **2a** using a catalytic amount of palladium acetate under Jeffery's conditions[9] for Heck-type coupling. Methyl isoquinolin-1-one-3-carboxylate **4** was the only product isolated (61%). The cinnamate **3a**, possibly formed as an intermediate (not isolated) must have undergone in situ cyclisation with the loss of the *N*-acetyl group (Scheme 1).

Oxoquinoline-3-carboxylic acids (ciprofloxacin, nalidaxic acid, norfloxacin and others) are well known antibacterial agents[10] and therefore synthesis of the corresponding isoquinoline analogues is of significance. On the other hand, the analogous reaction of 2-iodobenzaldehyde with the same olefin **2a** under identical conditions did not provide the expected methyl isoquinoline-3-carboxylate; instead the product was characterised as the 2-substituted benzyl alcohol **3b** (62%). Olefin **2b** similarly gave the reduced product **3c** under identical conditions. Apparently, in addition to the coupling, an unexpected reduction of the formyl group also took place. Various questions related to this unprecedented reduction remain unanswered at this moment. However, the observations that the formyl groups in 4-iodobenzaldehyde and benzaldehyde remained unaffected under identical conditions prompted us to believe that the reduction is possibly intramolecular in nature. Interestingly, the problem could be avoided by changing the reaction conditions. When the reaction of 2-iodobenzaldehyde with methyl 2-acetamidoacrylate **2a** was conducted in refluxing acetonitrile using triethylamine as base, palladium acetate (5 mol%) as catalyst and tri-*o*-tolylphosphine (10 mol%) as additive, a smooth conversion (68%) to methyl isoquinoline-3-carboxylate was observed. A two-step version of the same overall transformation proved to be higher yielding. Thus, from the coupling of the iodoacetal **1c** with each of the olefins **2a** and **2b**, the intermediate cinnamates **3d–e** were obtained in 87 and 91% yields, respectively. Simple treatment of these products **3d–e** with pyridinium *p*-toluenesulfonate (PPTS) or *p*-toluenesulphonic acid resulted in the formation of the desired isoquinoline-3-carboxylates (**5a–b**) in greater than 95% yield[11] (Scheme 2).

Isoquinoline-3-carboxylates and 1,2-dihydroisoquinoline-3-carboxylates are important compounds in view of their use in the synthesis of designed peptidomimetics.[12] Several syntheses including two recent ones[13] have been reported for the synthesis of isoquinoline-3-carboxylates. The simplicity of our method may complement those existing in the literature.[14]

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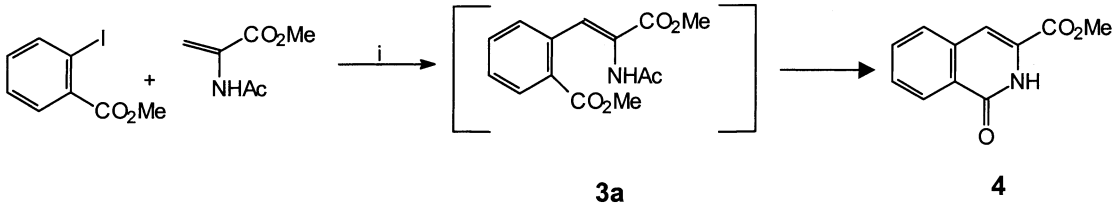
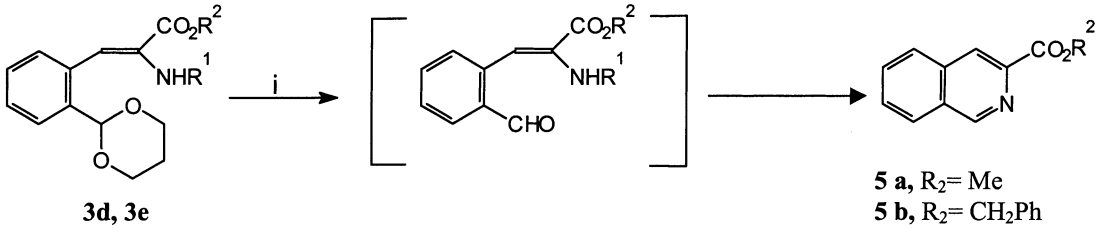


Scheme 1. *Reagents and conditions*: (i) $Pd(OAc)_2/n\text{-}Bu_4N^+Cl^-$/DMF/85–90°C/18 h.



Scheme 2. *Reagents and conditions*: (i) PPTS/acetone–water, 8:1/reflux/5–8 h.

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