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Synthesis of isoindolin-1-ones via palladium-catalyzed intermolecular coupling and heteroannulation between 2-iodobenzoyl chloride and imines

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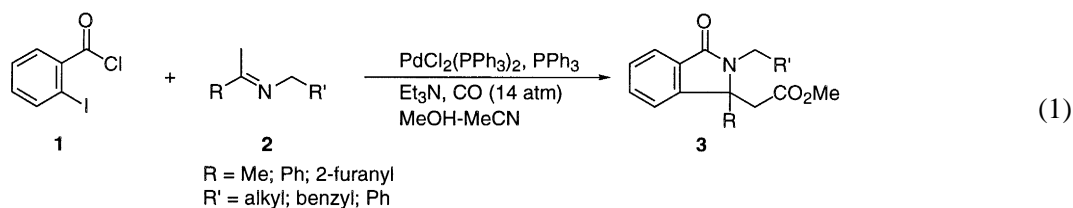
Abstract

2-Iodobenzoyl chloride reacts with an array of imines in acetonitrile–methanol under carbon monoxide pressure in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride/triphenylphosphine together with triethylamine to afford the corresponding isoindolin-1-ones in moderate yields. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: palladium; catalyst; cyclization; isoindolin-1-ones.

Palladium-catalyzed heteroannulation technology has been widely introduced for the formation of many heterocyclic compounds which play an important role as a basic skeleton for the design of many pharmacologically active compounds.¹ In connection with this report, it is well-known that several isoindolinones such as staurosporin, DN-2327, indoprofen, and 2-[4-(1-carboxypropyl)phenyl]isoindolin-1-one exert a broad spectrum of physiological activities.² Thus, many synthetic methods including transition metal-catalyzed versions have been reported for the formation of the structural core of isoindolinones. We recently developed and reported several palladium-catalyzed syntheses of diastereoselective tricyclic isoindolinones^{3–5} and various 3-substituted isoindolinones^{6–9} through intra- or intermolecular carbopalladative addition across carbon–nitrogen double bonds as an organometallic key step. As part of our continuing studies on palladium-catalyzed synthesis of isoindolinones, we here report the palladium-catalyzed synthesis of carbomethoxy functional group-induced isoindolin-1-ones from 2-iodobenzoyl chloride and an array of imines via intermolecular coupling, cyclization and carbonylation processes.

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We examined the intermolecular coupling and cyclization between 2-iodobenzoyl chloride (**1**) and imines **2** under a similar catalytic system which we introduced for the synthesis of several isoindolinones. From various imines **2** the corresponding isoindolin-1-ones **3** were produced in moderate yields, several representative results being summarized in Table 1. Table 1 indicates that the structural nature of the amine counterpart of the imines **2** showed no decisive influence on the formation of **3**. However, the structural nature of the ketone counterpart of **2** is important for the formation of **3**. We recently reported that **1** reacted with ketimines bearing a hydrogen attached to β -*sp*³-carbon to afford 3-vinyl- and spiro-isoindolinones by final β -hydrogen elimination.^{8,9} Thus, the imines examined for the present study were designed to intercept by an anion transfer reagent (CO/MeOH) instead of a β -hydrogen elimination of an alkylpalladium intermediate.¹⁰ As shown in Table 1, similar treatment of **1** with *N*-allylisopropylideneamine under an analogous catalytic system afforded tricyclic isoindolinone in 30% isolated yield.

Table 1
Palladium-catalyzed synthesis of isoindolin-1-ones from **1** and imines^a

Imine	Isoindolin-1-one	Yield ^b (%)	Imine	Isoindolin-1-one	Yield ^b (%)
		55			51
		56			51
		42 ^c			48
		48			30 ^d

^a All reactions were carried out with **1** (2 mmol), imine (2 mmol), PdCl₂(PPh₃)₂ (4 mol%), PPh₃ (8 mol%) and Et₃N (5 mmol) under CO (14 atm) in MeOH (4 mmol) and MeCN (10 mL) at 100 °C for 20 h except otherwise mentioned. ^b Isolated yield. ^c Ar = 2-furanyl. ^d In the absence of MeOH.

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