ChemComm

COMMUNICATION

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View Article Online View Journal | View Issue

Cite this: Chem. Commun., 2013, 49, 3254

Received 23rd January 2013, Accepted 27th February 2013

DOI: 10.1039/c3cc40577j

www.rsc.org/chemcomm

Palladium-catalyzed insertion of *N*-tosylhydrazones for the synthesis of isoindolines[†]

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Isoindolines are synthesized by palladium-catalyzed coupling reaction of *N*-(2-iodobenzyl) anilines with α , β -unsaturated *N*-tosylhydrazones. The reaction has several potential advantages: (1) toleration of a wide range of functional groups, (2) easy to handle and with mild conditions, (3) enriches the isoindoline family, (4) two new bonds form in one step.

Isoindolines and their derivatives display a variety of biological activities and interesting chemical properties. For instance, the isoindoline structure is present in molecules which act as modulators of estrogen, inhibitors of selective serotonin reuptake, spin probes for studying cancer, antitumor, herbicidal, anti-inflammatory and anesthetic agents.¹ Moreover, they play an important role in cycloaddition reactions and organic lightemitting diodes.² Therefore, the study of these compounds continues to be an area of great interest in organic chemistry. A variety of synthetic procedures have been reported, however, these methods usually suffer from long reaction time, high temperature, expensive catalysts or high catalyst loadings.³ In addition, the protecting groups on the nitrogen of the products of these methods are often Cbz, Boc, Ts,⁴ or the products can't allow for incorporation of aromatic moieties on the isoindoline ring,⁵ which limits the versatility of the isoindoline. Hence, development of new, efficient and straightforward methods for the preparation of diverse isoindolines is highly desirable.

Palladium-catalyzed insertion of diazo compounds has been shown to be a powerful method for the C–C bond-forming reaction, which is analogous to insertion of a CO. Migratory insertion of Pd carbene species is considered to be the key step for these crosscoupling reactions. A series of palladium-catalyzed reactions involving benzyl, vinyl, aryl and acyl group migratory insertion have been reported by Van Vranken, Barluenga and Wang *et al.*^{6–9} For example, migration of vinyl groups could generate η^3 -allylpalladium intermediates that can be trapped with nucleophiles such as secondary amines and sodium diethylmalonate.⁷ Previously, we verified that η^3 -allylpalladium intermediates can also be formed from palladium-catalyzed dediazotization of the arylvinyldiazoacetate, which is then attacked by amines.⁸ As we all know, *N*-tosylhydrazones could decompose to give unstabilized diazo substrates in the Bamford–Stevens reaction, which expanded the scope of palladium-catalyzed coupling reaction of diazo compounds.⁹ In this work we report a related coupling using α , β -unsaturated *N*-tosylhydrazones and *N*-(2-iodobenzyl) anilines to construct isoindoline derivatives.

We hypothesize that the reaction starts with oxidative addition of palladium to the *N*-(2-iodobenzyl) anilines to afford intermediate **A** (as shown in Scheme 1), which can dediazotize the diazo compound **B** (generated *in situ* from *N*-tosylhydrazone) to afford a palladium carbene complex **C**. Then, migratory insertion of the anyl group into the palladium carbene at the carbonic carbon atom leads to the η^1 -allylpalladium complex **D**, which can isomerize to the η^3 -allylpalladium **E**. The intermediate **E** species is then trapped



Scheme 1 Plausible catalytic cycle.

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[†] Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds. CCDC 918081 (**3**]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc40577j

Table 1 Optimization of conditions for the palladium-catalyzed reaction of 1a and $2a^{\rm a}$



Entry	Equiv. of 2a	Base	Solvent	Yield ²
1	1.75	<i>t</i> -BuOLi (4.75 equiv.)	THF	72
2	2.00	t-BuOLi (5.00 equiv.)	THF	77
3	2.25	t-BuOLi (5.25 equiv.)	THF	88
4	2.50	t-BuOLi (5.50 equiv.)	THF	88
5	2.25	t-BuOLi (5.25 equiv.)	THF	25^{c}
6	2.25	t-BuOLi (5.25 equiv.)	DCE	76
7	2.25	t-BuOLi (5.25 equiv.)	MeCN	52
8	2.25	t-BuOLi (5.25 equiv.)	Dioxane	85
9	2.25	t-BuOLi (5.25 equiv.)	Toluene	45
10	2.25	K_2CO_3 (5.25 equiv.)	THF	86
11	2.25	Cs_2CO_3 (5.25 equiv.)	THF	82
12	2.25	t-BuOK (5.25 equiv.)	THF	0
13	2.25	t-BuONa (5.25 equiv.)	THF	0
14	2.25	t-BuOLi (5.25 equiv.)	THF	0^d

^a Reaction conditions: 1a (0.3 mmol), Pd₂(dba)₃·CHCl₃ (2.5 mmol%), PPh₃ (15 mmol%), solvent (4 ml).
 ^b Yield of the isolated product.
 ^c 1.0 equiv. of BTAC used as an additive.
 ^d Without palladium catalysis.

with an amine nucleophile and the Pd(0) catalyst is regenerated with the aid of base.¹⁰

Initially, we studied the cross-coupling reaction by employing N-(2-iodobenzyl)-3,4-dimethylaniline 1a and N-tosylhydrazone 2a with Pd₂(dba)₃·CHCl₃/PPh₃ as a catalyst and *t*-BuOLi as base in THF at 60 °C (Table 1, entry 1). To our delight, the desired coupling product was isolated in 72% yield. Increasing the amount of lithium tert-butoxide and N-tosylhydrazone relative to 1a led to improvement in the yield (Table 1, entries 2 and 3). Using 2.25 equiv. of 2a gave a good yield but when the amount of 2a was increased to 2.50 equiv., the yield of 3a did not increase further (Table 1, entry 4). Then 1.0 equiv. of BTAC was used as an additive to enhance the solubility of the lithiated sulfonylhydrazone, but led to a diminished yield (Table 1, entry 5). Next, several other solvents, such as DCE, MeCN, dioxane and toluene, were examined, however, they were all less efficient than THF (Table 1, entries 6-9). Additionally, it was found that the yield could not be further improved by employing different bases (Table 1, entries 10-13). Various palladium catalysts including Pd(n) and Pd(0) were screened. From the results, Pd(OAc)₂ afforded good yield and PdCl₂(MeCN)₂ was isolated in low yield. As for Pd(0), both Pd₂(dba)₃ and $Pd(PPh_3)_4$ worked efficiently for this reaction. It is worth noting that the ligand PPh3 was essential for this reaction. Only a trace amount of product was detected when XPhos was employed as a ligand, and no reaction occurred in the absence of PPh₃ (for details, see the ESI⁺). Finally, the reaction could not proceed without palladium catalysis (Table 1, entry 14).

With the optimal conditions in hand, we examined the scope of this reaction with respect to the amine. The yield of isoindoline was dramatically affected by the nucleophilicity of the amine. Electron-donating groups led to moderate to good yields (Scheme 2, 3a–d); however, the electron-withdrawing group gave a lower yield, which may be due to less nucleophilicity of the



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 Scheme 2
 Palladium-catalyzed cross-coupling of N-(2-iodobenzyl) aniline derivatives with N-tosylhydrazones. Reaction conditions: 1 (0.3 mmol), 2 (0.675 mmol, 2.25 equiv.), t-BuOLi (1.575 mmol, 5.25 equiv.), THF (4 ml), Pd₂(dba)₃·CHCl₃ (2.5 mmol%), PPh₃ (15 mmol%), 60 °C, 4.5–5.5 h. Yield of the isolated product.

amine (Scheme 2, **3f**). In the case of \mathbb{R}^1 , both electron-donating and electron-withdrawing groups were well suited on the aromatic ring (Scheme 2, **3g-k** and **3s**), except **3q**, which contains an *ortho*substituent. Notably, the halogen substituents are tolerated under the Pd-catalyzed conditions (Scheme 2, **3g-i**), which allows further transition-metal-catalyzed coupling reaction. As for the *N*-tosylhydrazones, a series of substituents and functional groups, including phenyl, heterocycle and *ortho*-substituted *N*-tosylhydrazones, could react smoothly with *N*-(2-iodobenzyl)-3,4-dimethylaniline **1a** to afford the corresponding isoindolines in moderate to good yields (Scheme 2, **3l-p**, **3r** and **3t**). The structure of **3l** was further established by X-ray diffraction.



Scheme 3 Palladium-catalyzed cross-coupling of **1a** with non-aromatic *N*-tosyl-hydrazones. ^a2.0 equiv. of NEt₃ was used as co-base, *t*-BuOLi was decreased to 3.25 equiv.

To further expand the scope of the reaction, we investigated non-aromatic α,β -unsaturated *N*-tosylhydrazones (Scheme 3). To our disappointment, when the H-substituted *N*-tosylhydrazones were used as substrates under the standard conditions, the desired product was obtained in poor yield. In pioneering studies, Van Vranken and co-workers demonstrated that triethylamine used as co-base in palladium-catalyzed reaction of diazo compounds proved useful for carbenylative aminations. Indeed, when 2.0 equiv. of NEt₃ was added, it resulted in 53% yield. While as for methyl-substituted α,β -unsaturated *N*-tosylhydrazones a similar yield was afforded both in the presence and absence of Et₃N.

In summary, we have reported a new, efficient and straightforward method for the synthesis of isoindolines by palladiumcatalyzed coupling reaction of *N*-(2-iodobenzyl) anilines with tosylhydrazones derived from α , β -unsaturated aldehydes. The reaction has several potential advantages: (1) a wide range of functional groups are tolerated and the yields are moderate to good. (2) The reaction is easy to handle and the conditions are mild. (3) By changing the substituent on the protecting groups of the nitrogen and aromatic moieties on the isoindoline ring, a series of products with diverse substituents were synthesized, which enriched the isoindoline family. (4) Two new bonds are formed in a one-step reaction. Future work on three-component coupling reaction involving aryl halide, amine and vinyl hydrazone is in progress and will be reported in due course.

We thank the National Science Foundation (NSF 21072080 and 21272101) and National Basic Research Program of China (973 Program) 2010CB833203 and "111" program of MOE and PCSIRT: IRT1138 for financial support. Lian-Biao Zhao thanks the Natural Science Foundation of Gansu (No. 096RJZA006) PRC for supporting this study.

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