Facile ligand-free Pd-catalyzed tandem C–C/C–N coupling reaction: a novel access to highly diverse tetrazole tag isoindoline derivatives

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Abstract
A novel and robust route for the synthesis of diversely substituted isoindoline skeletons through a ligand-free Pd-catalyzed cascade consisting of isocyanide insertion into Ugi-tetrazole has been developed. The tetrazole precursor is prepared in one step by the Ugi-four component reaction. The reaction proceeds smoothly under mild conditions with high efficiency. This chemistry is simple, economical, and is believed to be the key step during the synthesis of significant pharmaceuticals.

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Introduction

The isoindolines and 1-substituted isoindolin-3-ones nuclei are substructures present in many natural products such as fumaridine and lennoxamine.1–3 and the core skeleton of some biologically active compounds (Fig. 1).4 These heterocyclic frameworks have attracted considerable attention in synthetic organic and medicinal chemistry due to their broad structural diversity and broad-spectrum biological activities, including: Endothelin-A Receptor Antagonists,5 inhibition of prolyl dipeptidase DPP8,6 PPARδ agonists,7 histone deacetylase inhibitors,8 inhibitors of selective serotonin reuptake,9 diuretic, NMDA receptor antagonists, herbicidal,10 anti-inflammatory, and antileukemic agents.11 Furthermore, isoindolines inhibit the amyloid protein aggregation which demonstrate a potency in the treatment of Alzheimer's disease, the ligand affinity for the melanocortin subtype-4 receptor (MC4R) (D), act as multidrug resistance reversal agents, and fibrinogen receptor antagonists.12,13 On the other side, tetrazole is an extremely valuable scaffolds due to their diverse biological activity.14

A variety of synthetic procedures have been reported for the preparation of isoindoline core structural skeletons.15 However, most of them usually require the use of expensive starting materials/catalysts or high catalyst loadings, suffer from long reaction time, difficulty in workup, high temperature, and with fewer points of diversity.16 Hence, the fascinating biological profiles of this group of compounds has spurred organic chemists to devise new, efficient, and straightforward methods for their viable preparation with increased molecular diversity and complexity.

Transition metal catalyzed synthesis of substituted isoindoline analogues has received noteworthy attention.17 In this perspective, palladium catalysis is of undisputed importance in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. In the recent past, synthesis of biologically important heterocycles by isocyanide insertion under palladium catalysis is an efficient but relatively unexplored method.18

Due to the presence of a formally divalent carbon atom, isocyanides have been recognized as powerful building blocks for constructing functional molecules with increased molecular diversity for drug discovery and natural product synthesis.19 On the other hand, isocyanides serve not simply as a carbon monoxide equivalent but also as a unique C1 source to substitute the well-known CO insertions, such as more practical handling and an extra diversity point for scaffold embellishment.20
In the past few years, we have been involved in the multicomponent Ugi reactions for generation of natural product-like compounds,21 the chemistry involving palladium-catalyzed isocyanide insertion,22 and new strategies for the diversity oriented synthesis of biologically important heterocycles.23 Based on these observations, herein, we report the ligand-free Pd-catalyzed coupling cascade with the insertion of isocyanide into amine precursors, which was obtained by modified TMSN₃-Ugi MCR for the construction of isoindoline derivatives.24 To the best of our knowledge, it is the first Letter to the synthesis of diverse isoindoline and isoindolinone derivatives.

**Results and discussion**

As shown in Scheme 1a, we portray a rapid construction of a series of 1,5-disubstituted-1H tetrazoles (9–19) with good to excellent overall yields (79–95%) utilizing a catalyst free optimized modified Ugi 4-CR process employing commercially available aldehydes 6, amines 7, isocyanides 8, and TMSN₃ in MeOH. The mechanistic pathway for the synthesis of isoindoline precursors has been shown in Scheme 1b.25 The first step initiates with the formation of imine (a) by the reaction of amine and aldehydes. The imine (a) converts into iminium (b), which give nucleophilic addition with isocyanide to form intermediate (c). After azide insertion intermediate (c) gives isoindoline precursors. The corresponding isoindoline precursors, which were used as a starting substrate for the ligand-free palladium-catalyzed cascade reaction involve insertion and intramolecular cyclization of an isocyanide. Further as depicted in Scheme 2, there can be formed two probable products A and B of the same molecular weights under Pd-catalyzed conditions.1H NMR,13C NMR, and 2-D NMR data of compound 20 confirmed that the products have the general structure B, which; was unusual from normal probable product A.26

In an initial attempt, amine precursor 9 was used as a model compound for the reaction with tert-butyl isocyanide (8a) to screen the reaction conditions with a variety of bases, catalyst, and solvents (Table 1). After extensive screening of the reaction parameters, the optimal reactions that were found to involve Pd(OAc)₂ (5 mol %), Cs₂CO₃ (1.5 equiv) in DMF (2 mL) at 90 °C were identified (Table 1). The desired product (E)-N-(3-(1-tert-butyl-1H-tetrazol-5-yl)-2-(4-methoxybenzyl)isoindolin-1-ylidene)-2-methylpropan-2-amine (20) was obtained in 70% yield. No reaction...
occurred, and the starting substrate 9 remained intact when palladium was excluded (Table 1, entry 1). Among the two catalysts PdCl₂ and Pd(OAc)₂ used, Pd(OAc)₂ was found to be the best and provided the product 20 in 70% yield when the reaction was run in DMF as a solvent at 90 °C (Table 1, entry 3). In the presence of the Pd(OAc)₂ catalyst (5 mol %), no desired product was observed without any base (Table 1, entry 4). On the other hand PdCl₂ resulted in moderate yields of 20 (Table 1, entries 2). Also, various bases K₂CO₃, K₃PO₄, Na₂CO₃, NaHCO₃, and KOtBu were tested and the best result was obtained when Cs₂CO₃ (1.5 equiv) was utilized as the base, affording 20 in 70% yield (compare entries 5–9 and 3 Table 1) in DMF at 90 °C. Using Pd(OAc)₂ as the catalyst and Cs₂CO₃ as the base in DMSO resulted in a slightly lower yield (Table 1, entry 10), while using toluene and dioxane under the same conditions provided 20 in only poor yields (Table 1, entries 11 and 12). The reaction proceeded to completion in 1 h under heating conditions at 90 °C. Further attempts to optimize the isocyanide insertion, including increasing the catalyst loadings,
Table 2
Scope of the two step procedure

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>IMCR products yield (%)</th>
<th>Coupling products yield (%)</th>
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<td>20 70%</td>
</tr>
<tr>
<td>2</td>
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<td>10 85%</td>
<td>21 72%</td>
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<tr>
<td>4</td>
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<td>23 74%</td>
</tr>
<tr>
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<td>13 80%</td>
<td>24 67%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>14 89%</td>
<td>25 70%</td>
</tr>
<tr>
<td>Entry</td>
<td>Starting material</td>
<td>IMCR products yield(^a) (%)</td>
<td>Coupling products yield(^b) (%)</td>
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<tr>
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<td><img src="image" alt="Entry 7" /> 26 68%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Entry 8" /></td>
<td><img src="image" alt="Entry 8" /> 16 79%</td>
<td><img src="image" alt="Entry 8" /> 27 72%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Entry 9" /></td>
<td><img src="image" alt="Entry 9" /> 17 88%</td>
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<tr>
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<tr>
<td>12</td>
<td><img src="image" alt="Entry 12" /></td>
<td><img src="image" alt="Entry 12" /> 19 82%</td>
<td><img src="image" alt="Entry 12" /> 31 65%</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: substrate 9 (1 equiv), Pd(OAc)\(_2\) catalyst (5 mol %), Cs\(_2\)CO\(_3\) (1.5 equiv), DMF (2 mL), 90 °C, 1 h.

\(^b\) Isolated yield after column chromatography.
different type of ligands (DPPE, Xphos, and PPh₃), and temperature of the reaction, did not improve the yield of the reaction.

With this result in hand, we next investigated the scope of the reaction to other amines precursors (9–19) and isocyanides. Reactions furnish the corresponding tetrazole–isoindolines (20–31, Scheme 2) in moderate to good yield. The amine precursors (9–19) were synthesized from the different substituted benzaldehydes, various amines and isocyanides via different Ugi-MCR in excellent yields. Interestingly, various substituted amines including different types of benzylamine, alkyl amines (n-butylamine and iPr₂NH), and aniline were examined in the reaction, and the corresponding products were furnished in good yields. Whatever the group at the amine nitrogen in the tetrazole compounds did not affect significantly on the yields of final products. Other isocyanides such as 1,1,3,3-tetramethylbutyl isocyanide and cyclohexyl isocyanide were also tried in the meantime but only tert-butylisocyanide was found to effectively undergo insertion and 1,1,3,3-tetramethylbutyl isocyanide was moderately effective and yielded the desired compound (29) in good yield (71%). Hence, tert-butylisocyanide was the only isocyanide used for the reaction optimization. Additionally, the reaction can also be conducted with N-benzyl-1-(1-tert-butyl-1H-tetrazol-5-yl)-1-(2-iodophenyl)methanimine (18) and 1-(1-tert-butyl-1H-tetrazol-5-yl)-1-(2-iodophenyl)-N-(4 methoxybenzyl)methanimine (19). As expected, the reaction time of Ugi-MCR synthesized amine precursor was same and the desired products (30 and 31) were furnished in satisfactory yields (see Table 2).

The ¹H and ¹³C NMR signal assignments and connectivity of compound 21 were determined from a combination of ¹³C, DEPT 135, DEPT 90, COSY, HSQC, and HMBC data and spatial correlations are established by NOESY. COSY correlations established the spin systems, which were H-3, H-4, H-5, and H-6 in ring-B and H-2, H-3, H-5, and H-4' in ring-D. H-3 and H-5 of ring B is giving a HMBC correlation with C-7 and H-4 and H-6 are giving HMBC correlations with C-8. The characteristics carbon atom C-2 at δ 100.4 ppm showed HMBC correlations with benzylic protons and H-3 which established the connectivity between the benzyl moiety and ring B to the ring A through N-1 and C-7, C-8, respectively. The NOE correlation between 12-(CH₃), protons and H-6 strengthened the possibility of an E configuration of the compound (Fig. 2).

The presence of N–H proton in compound 20 was verified by D₂O shake experiment. During D₂O shake experiment of compound 20, an unexpected change in ¹H NMR spectrum was observed which indicated that compound 20 got degraded. Interestingly, the intensity of protons peak of compound 20 was diminished and a new peak pattern was observed in the ¹H NMR spectrum and each peak seemed to be double. Similar double peak pattern was observed in the ¹³C NMR spectrum also. In the ¹³C NMR spectrum one characteristic peak appeared at δ 167.73 ppm and peak at δ 100.45 ppm was diminished. After getting this information from NMR data, we analyzed this NMR sample and found that there were three spots on the TLC at this stage, whereas there were only one spot on the TLC before starting the D₂O shake experiment. So, it was assumed that moisture or D₂O played a significant role in the conversion of 20 into 32. With the help of 1D and 2D NMR data (¹H, ¹³C, DEPT135, DEPT90, COSY, HSQC, HMBC, and NOESY), the observed compound was characterized as (E)-3-(tert-butylimino)-2-(4-methoxybenzyl)isoindolin-1-one (32). It’s also confirmed by single crystal X-ray analysis of representative compounds 32 (Fig. 3, CCDC No-959960). In crystal X-ray analysis, we observed...
the oxygen atom which replaced the tetrazole ring in compound 32 via hydrolysis (Scheme 3).

The $^1$H and $^{13}$C NMR signal assignments and connectivity were determined from a combination of various 1D and 2D NMR experiments and spatial correlations are established by NOESY. COSY correlations established the spin systems, which were H-3, H-4, H-5, H-6 in ring-B, and H-2,6’ and H-3,5’ in ring-C. H-3 and H-5 of ring B is giving a HMBC correlation with C-7 and H-4 and H-6 are giving HMBC correlations with C-8. Further H-3 and H-6 are giving HMBC correlations with C-2 and C-9, respectively, and established the connectivity of ring A and B. The important HMBC correlations of benzylic protons to C-2 and C-9 clearly indicated that the substituted benzylic connected to ring A through N-1. The important NOE correlation between 12-(CH$_3$)$_3$ protons and H-6 showed the proximity of both protons in space and this NOE correlation showed the E configuration of the compound (Fig. 4).

We propose the mechanism for the synthesis of (E)-N-(3-(1-tert-butyl-1H-tetrazol-5-yl)-2-(4-methoxybenzyl)isoindolin-1-ylidene)-2-methylpropan-2-amine of type 20 was depicted in Scheme 4. The Palladium(0) species undergoes oxidative addition to the C–Br bond of amine precursor 9 leading to the intermediate 34 which on insertion of tert-butyl isocyanide leads to Pd(II) species 35. Intermediate 35 via intramolecular cyclization provides species 20.

Conclusions

In summary, we have demonstrated an efficient method for the synthesis of tetrazole–isoindoline via palladium-catalyzed cyclization with isocyanide insertion for the first time. The reactions are operationally simple and has several potential advantages: (1) toleration of a wide range of functional groups and the yields are moderate to good, (2) the reaction is easy to handle and the conditions are mild, (3) enriches the isoindoline family, (4) two new bonds are formed in a one-step reaction. We expect that the novel transformation can be used for further development of new isocyanide based catalytic reactions. Further studies on the scope of this novel process and the synthetic use of the nitrogen-containing heterocycles are currently underway.
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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tlet.2015.08.008.

References and notes