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Synthesis of N-substituted carbazolones from α-iodo enaminones via Pd(0)-catalyzed intramolecular coupling under microwave irradiation

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ABSTRACT

A variety of *N*-aryl and *N*-alkyl carbazolones were conveniently achieved in good to high yields via $Pd_2(dba)_3$-mediated intramolecular coupling of N-substituted α-iodo enaminones under microwave irradiation. The Pd(0)-catalyzed cyclization was found to proceed favorably with the more electron-deficient phenyl ring during the reactions involving unsymmetrical *N*,*N*-diaryl α-iodo enaminones. This unique property enables the construction of carbazolone skeleton containing nitro substituted benzenoid ring.

N-Substituted carbazolone moieties, including both N-alkylated and N-arylated ones, have been found as important basic building blocks in many synthetic drugs,[1] natural products,[2] and biologically active compounds.[3]

Generally, the N-substituted carbazolones can be synthesized from N-unsubstituted carbazolones via base-mediated alkylation[4] or S_NAr arylation.[5] Alternatively, N-substituted enaminones provide an expedient access to N-substituted carbazolones via C–C bond formation.[6,7] For example, Fisher indole synthesis was applicable to the synthesis of *N*-phenyl and *N*-aroyl carbazolones (Fig. 1, path a).[8] Surprisingly, literature survey indicates that this approach has never been applied to the synthesis of *N*-alkyl carbazolones. Another method that can also lead to the formation of carbazolone ring, is the Heck reaction, via Pd(0)-mediated C–C bond formation (Fig. 1, path b).[9] However, this approach is seldom applied to the synthesis of *N*-aryl carbazolones, possibly because the N-arylation of the enaminone substrates at an early stage is not a desirable process. The third commonly applied method is by the direct oxidative C–C coupling through palladium-catalyzed[6] or photochemical reaction,[7] which is considered as a powerful tool for the carbazolone formation since no halogen atom is needed for the cyclization to occur (Fig. 1, path c). However, this method also suffers its limitation in synthesis of *N*-aryl carbazolones.

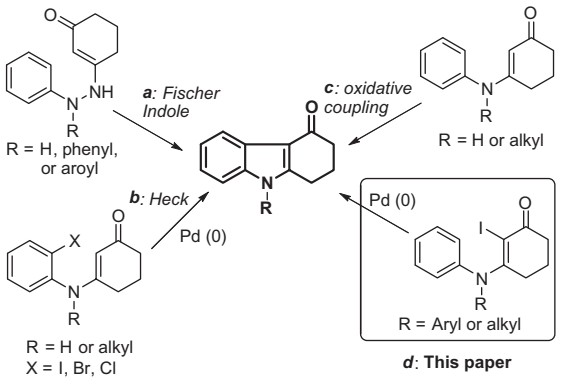

Figure 1. Methods for the formation of carbazolone skeletons via the strategy of C–C bond formation.

Herein, we report an alternative synthesis of N-substituted carbazolones, including both *N*-aryl and *N*-alkyl carbazolones, from N-substituted α-iodo *N*-aryl enaminones[10] via Pd(0)-catalyzed intramolecular coupling. Differing from the classical Heck substrates,[9] the iodo substituent in the reactants is substituted on the α-position of the cyclohexenone ring, rather than the phenyl ring, in our reaction (Fig. 1, path d).

In our previous work, we described the formation of a variety of *N*-aryl α-iodo enaminones **3**, obtained in high yields from the readily available 3-aminocyclohex-2-enones via concurrent α-iodination and N-arylation mediated by $ArI(OAc)_2$ (**2**) (see Scheme 1).[10]

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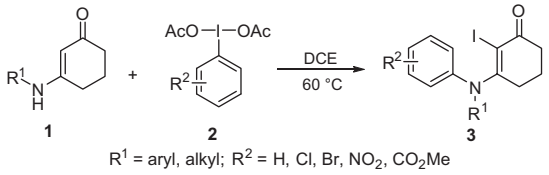
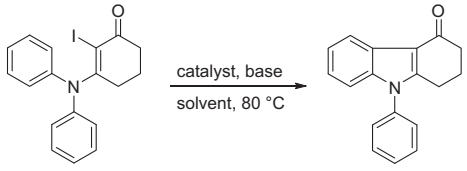


Scheme 1. Formation of N-substituted α-iodo enaminones **3** from enaminone 1 and $ArI(OAc)_2$ **2.**

Building on this work, we launch the research of finding new methods to convert these *N*-aryl and *N*-alkyl α-iodo enaminones **3** to the more useful carbazolone derivatives through ring closure via palladium(0)-mediated intramolecular C–C bond formation.[11]

We began our investigation by carrying out an extensive screening of the variables to identify the optimal conditions for this conversion. Considering that the N-substituted α-iodo enaminones **3** in our study are similar to the substrate in Heck reactions, we selected $Pd_2(dba)_3$ as the initial catalyst in anticipation of a similar oxidative insertion of the generated Pd(0) species into the C–I bond in the first step. Our experiments revealed that substrate **3a** indeed, underwent cyclization in the presence of $Pd_2(dba)_3$ and KOH in dry DMF,[12] albeit the desired product **4a** was obtained in only 12% yield (entry 1, Table 1). Encouraged by this initial result, we continue our research by investigating a variety of other bases (Table 1, entries 2–4). To our pleasant surprise, a good isolated yield of 70% of the desired product was achieved when Et_3N was used as base and the reaction heated at 80 °C for 12 h (Table 1, entry 4). Further solvent screening study showed that none of the other solvents, including DMA, CH_3CN, Et_3N, dioxane, or toluene provide any better result (Table 1, entries 5–9). Considering that the reaction was heated at 80 °C for 12 h, we thought that the application of microwave irradiation[13] might shorten the reaction time and therefore improve the yield by minimizing the formation of byproducts. A gratifying 91% yield was successfully achieved by carrying out the reaction under microwave irradiation (400 W, 80 °C) for 30 min (Table 1, entry 11). Further attempts to improve either the catalytic activity or the yield with other palladium reagents were unsuccessful (Table 1, entries 11–15).

Table 1
Reaction condition optimization for the intramolecular cyclization of 3-(diphenylamino)-2-iodo-cyclohex-2-enone **3a**[a]



3a **4a**

Entry	Pd catalyst	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd_2(dba)_3$	KOH	DMF	1	12
2	$Pd_2(dba)_3$	K_2CO_3	DMF	1	10
3	$Pd_2(dba)_3$	KOAc	DMF	1.5	25
4	$Pd_2(dba)_3$	Et_3N	DMF	12	70[c]
5	$Pd_2(dba)_3$	Et_3N	DMA	12	65
6	$Pd_2(dba)_3$	Et_3N	CH_3CN	12	30
7	$Pd_2(dba)_3$	Et_3N	Et_3N	12	<5[d]
8	$Pd_2(dba)_3$	Et_3N	Dioxane	12	20
9	$Pd_2(dba)_3$	Et_3N	Toluene	12	<5
10[e]	$Pd_2(dba)_3$	Et_3N	DMF	0.5	91
11[e,f]	$Pd(OAc)_2/PPh_3$	Et_3N	DMF	0.5	43
12[e,f]	$PdCl_2/PPh_3$	Et_3N	DMF	0.5	85
13[e,f]	$PdCl_2$/dppf	Et_3N	DMF	1.0	34
14[e,f]	$PdCl_2$/dppe	Et_3N	DMF	0.5	<5
15[e,f]	$PdCl_2$/BINAP	Et_3N	DMF	0.5	10

[a] Reaction conditions: **3a** (0.26 mmol), Pd catalyst (5 mol%) and base (0.65 mmol) in 300 μL of solvent at 80 °C.
[b] Isolated yields.
[c] 82% conversion.
[d] 18% conversion.
[e] Under microwave irradiation (400 W, 80 °C).
[f] 15 mol% of ligand was used.

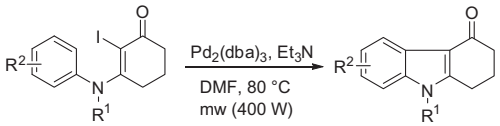
Under the optimized reaction conditions (Table 1, entry 10), the scope of this transformation was investigated. Results in Table 2 show that this catalytic system displays great tolerance to a variety of functional groups such as chloro, bromo, nitro, methyl, methoxy, and ester substituents on the phenyl ring in the substrates. Enaminones without any substituent on the phenyl rings can undergo cyclization smoothly to furnish *N*-phenyl carbazolones **4a** and **4b** in high yields (Table 2, entries 1–2). The enaminone substrates bearing weak electron-withdrawing substituents such as chloro and bromo groups at the phenyl ring also afforded the corresponding carbazolone products in good yields (entries 3–4, Table 2). When the unsymmetric *N*,*N*-diaryl α-iodo enaminone **3e** was applied, it was found that the cyclization occurred exclusively with the unsubstituted phenyl ring to give product **4e** in good yield (Table 2, entry 5), which implies that this Pd(0)-mediated cyclization process does not favor the electron-rich phenyl ring. Similarly, for the unsymmetric methoxy-substituted substrate **3f,** the electron-rich phenyl ring was inert and the cyclization afforded carbazolones **4f** as the sole product (entry 6, Table 2).

In the previous synthesis of carbazolones, the enaminone substrates bearing the nitro group on the phenyl ring seldom underwent the Pd-mediated annulation.[14] Remarkably, our reaction is applicable to the α-iodo enaminones that bear strong electron-withdrawing groups such as nitro group. For example, the desired cyclized product **4g** can be obtained from nitro-substituted substrate **3g** in 30% yield (Table 2, entry 7), along with the formation of the 3-(bis(4-nitrophenyl)amino)phenol as the major byproduct.[15] In addition to the similar byproduct resulted from the dehalogenative aromatization of iodo cyclohexenone,[15] the *para*-nitro substituted enaminone **3h** was found to selectively give *N*-phenyl carbazolone **4h** as the sole cyclized product, which further indicates that this cyclization process favors the more electron-deficient phenyl ring (entry 8, Table 2). Moreover, enaminone **3i** bearing the *meta*-nitro substituent afforded **4i** as the only regioisomer and in a relatively better yield (Table 2, entry 9). Considering that the unexpected aromatization was always the concomitant side reaction for these nitro-substituted enaminones, we came to use the nitro-substituted enaminone **3j**, with two methyl groups substituted on the same carbon of the cyclohexenone ring, in the hope of preventing the side reaction of aromatization. As expected, the desired cyclized **4j** was formed in a satisfactory 70% yield (Table 2, entry 10).

This method can also be used in synthesizing *N*-heteroaryl carbazolone compounds. α-Iodo enaminone **3k**, in which one phenyl ring is replaced by a substituted thienyl ring, was also converted to the carbazolone product **4k** in moderate yield under the conditions (entry 11, Table 2). Notably, the reaction was also applicable to the preparation of *N*-alkyl carbazolones. Subjecting *N*-alkyl α-iodo enaminone **3l** and **3m** to the identical conditions was found to give the corresponding *N*-alkyl carbazolones **4l** and **4m**, respectively, in good yields (Table 2, entries 12–13).

The scope of the substrates can be further broadened by changing the cyclohexenone ring to a five-membered cyclopentenone ring or seven-membered cycloheptenone ring. Homologues **6a** and **6b** could be accessed from the corresponding α-iodo enaminones **5a** and **5b**, respectively. However, the yields were inferior to that of **4a**, which possibly resulted from the higher ring strain existing in substrates **5a** and **5b**, and even more so in products **6a** and **6b** (Scheme 2).

Table 2
Synthesis of N-substituted carbazolones **4**[a]



3 **4**

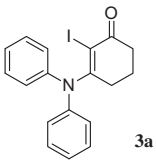
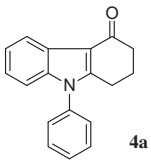
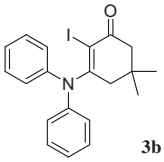
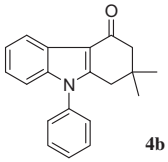
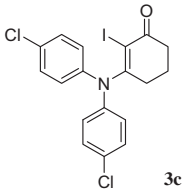
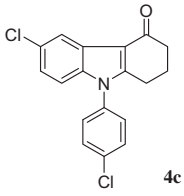
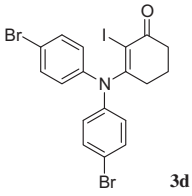
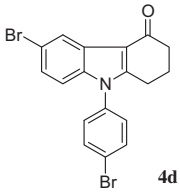
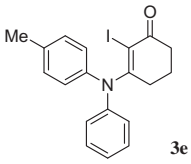
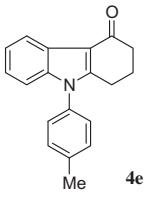
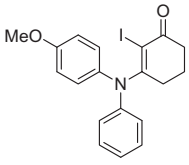
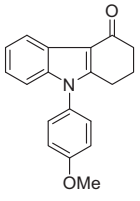
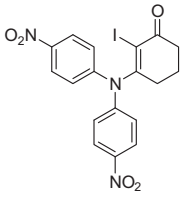
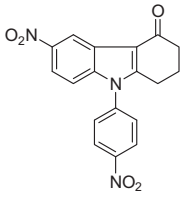
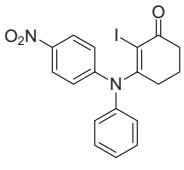
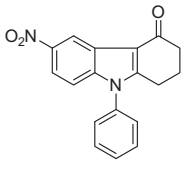
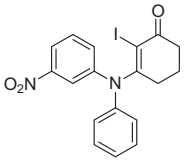
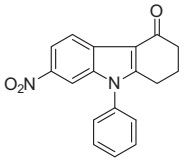
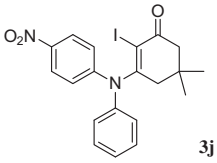
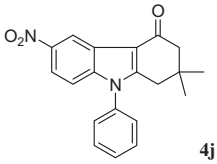
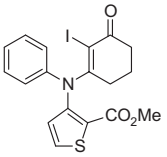
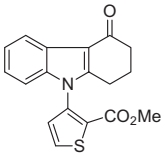
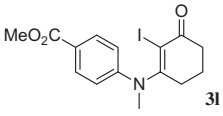
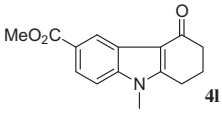
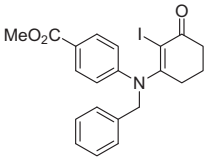
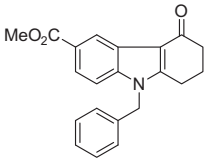
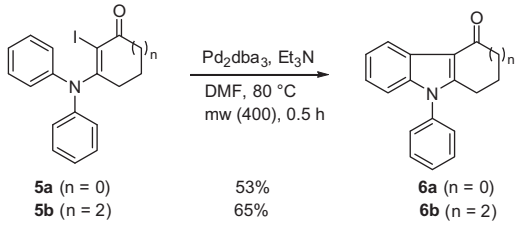
Entry	Enaminones **3**	Carbazolones **4**	Yield[b] (%)
1	 **3a**	 **4a**	91
2	 **3b**	 **4b**	88
3	 **3c**	 **4c**	87
4	 **3d**	 **4d**	77
5	 **3e**	 **4e**	80
6	 **3f**	 **4f**	75
7	 **3g**	 **4g**	30
8	 **3h**	 **4h**	45

Table 2 (*continued*)

Entry	Enaminones **3**	Carbazolones **4**	Yield[b] (%)
9	 **3i**	 **4i**	60
10	 **3j**	 **4j**	70
11	 **3k**	 **4k**	65
12	 **3l**	 **4l**	80
13	 **3m**	 **4m**	84

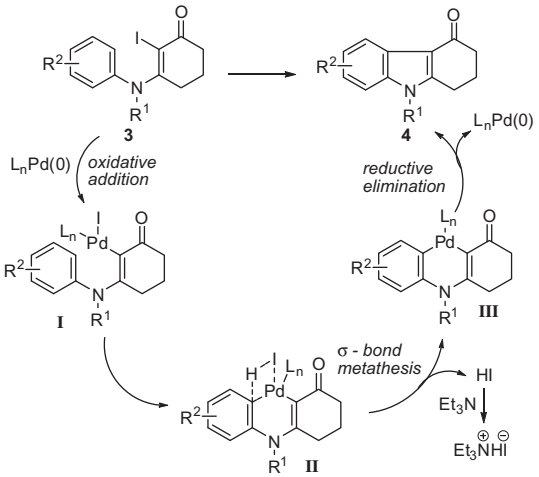
[a] Reaction conditions: **3** (0.26 mmol), $Pd_2(dba)_3$ (5 mol %), and Et_3N (0.65 mmol) in 300 μL of dry DMF at 80 °C under microwave irradiation (400 W) for 30 min.
[b] Isolated yields.



Scheme 2. Further application of the method for the synthesis of carbazolone homologues.

We propose that this Pd(0)-mediated cyclization process adopts the mechanistic sequence shown in Scheme 3.[16] Initially, the oxidative insertion of Pd(0) into the C(sp^2)–I bond leads to intermediate **I**. Then, the activation of the aromatic C–H bond takes place via σ-bond metathesis (through the transition state of **II**) to generate the six-membered palladium complex **III**, with the released HI being neutralized by Et_3N.[6c] Finally, reductive elimination occurs to afford the carbazolone products and regenerate the reactive Pd(0) species. An alternative mechanistic pathway involving electrophilic aromatic palladation[17] was not proposed since the corresponding carbocation intermediates generated are unstable for these nitro-substituted substrates.[14b]

Our experimental results clearly demonstrate that the Pd(0)-mediated cyclization is preferential to the more electron-deficient aryl rings. We tentatively propose that the acidity of the aromatic C(sp^2)-H in intermediate **II** is the key factor that determines this regioselectivity: the more acidic aromatic C(sp^2)-H enables a fast



Scheme 3. Plausible reaction mechanism.

σ-bond metathesis in intermediate **II**. The reason for the inferior yield of **4h**, compared with **4i**, is likely due to the fact that the aromatic C(sp^2)-H substituted at the *meta* position is less acidic than that at the *para* position.

In summary, we have developed an alternative and complementary approach to the synthesis of N-substituted carbazolones via Pd(0)-catalyzed intramolecular coupling of α-iodo enaminones.[18] The protocol can provide both *N*-aryl and *N*-alkyl carbazolones with various substitution patterns in good to excellent yields. Notably, the unique regioselectivity displayed in this

method enables the synthesis of carbazolone skeleton containing a nitro-group substituted benzenoid ring.

Acknowledgments

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Supplementary data

Supplementary data (list of new compounds along with their yield and copies of ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.009. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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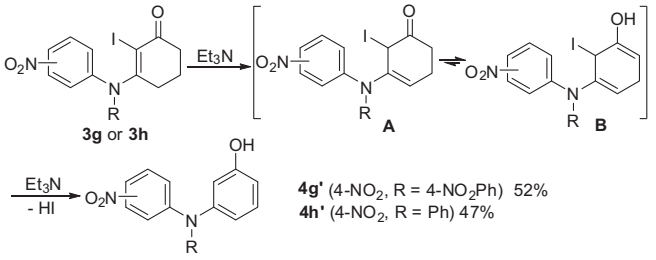

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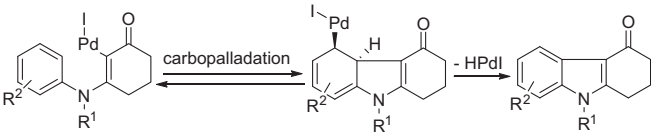

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18. *General procedure for the Synthesis of N-substituted carbazolones* ***4a–m*** *and* ***6a–b***: A mixture of α-iodo enaminones **3a–m**, **5a–b** (0.26 mmol), $Pd_2(dba)_3$ (5 mol %), Et_3N (0.65 mmol), and anhydrous DMF (300 μL) was stirred at 80 °C under microwave (400 W) for 30 min. After the consumption of the starting material, the mixture was cooled to room temperature, filtered to remove the solid materials. The filtrate was extracted with EtOAc (20 mL × 3). The organic phase was combined, dried with anhydrous Na_2SO_4, and evaporated to remove the solvent. The residue was purified by flash column chromatography (EtOAc/PE) on silica gel to give the desired products **4a–m**, **6a–b**.