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New Heck coupling strategies for the arylation of secondary and tertiary amides via palladium-catalyzed intramolecular cyclization

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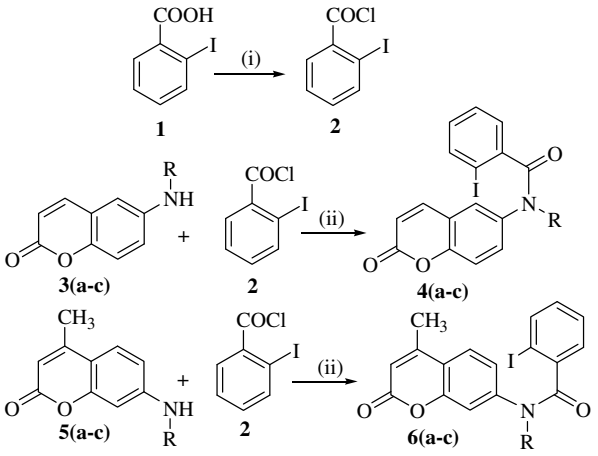
Abstract

A new synthetic protocol has been developed for the arylation of secondary and N-alkylated amide Heck precursors by the implementation of the palladium-catalyzed intramolecular Heck reaction strategies.

Keywords: Biaryl coupling; Heck reaction; Intramolecular cyclization; Amino coumarin; Palladium catalysts; Amide

The search of new methods for the construction of organic molecules from simple starting materials is an ongoing challenge for the organic chemists. Intramolecular aryl–aryl coupling reactions involving a palladium reagent have been used to synthesize many condensed heteroaromatic compounds.[1–6] A number of protocols have been developed for the synthesis of condensed heteroaromatic compounds using biaryl coupling reaction with palladium reagents[7–12] by the regioselective C–H bond activation with the intramolecular coordination of the amine to palladium.[13–16] It has been reported[17,18] that the palladium-catalyzed cyclization by the implementation of the intramolecular Heck reaction had failed where a secondary amide was used as the starting material. Recently, Trauner and co-workers, reported[19] a concise synthesis of rhazinilam through direct palladium-catalyzed intramolecular cyclization, with the MOM amide protecting starting material, for the success of this cyclization. They observed only deiodination with the free amide. Ripper and co-workers,[20] also attempted the same type of reaction with the secondary amide; but their attempts to carry out the palladium-catalyzed cyclization reaction using secondary amide as the starting material afforded no indication of the cyclization product. Subsequently Joseph and co-workers,[21] tried the reaction and their attempts of Heck reaction of free amide or *N*-methyl derivatives of the secondary amide led to low yields of the cyclized product (15–17% yields). Therefore, the above-mentioned findings have prompted us to undertake a study of the Heck reaction on the free amide or *N*-alkyl protected amide as the starting materials, with a view to synthesize the condensed heteroaromatic



Scheme 1. Reagents and conditions: (i) DCM, DMF, $(COCl)_2$, 0 °C, 30 min; (ii) DCM, Et_3N, DMAP, rt, 2 h. R = Et, Me, H.

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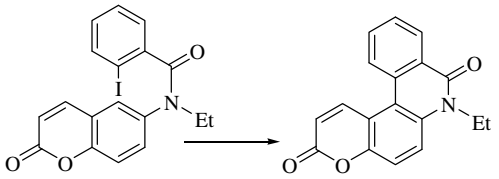
compounds. Additional interest is derived from our long standing efforts on the synthesis of heterocycles with bioactive moieties, and the coumarin system is well known for its bioactivity.[22–28]

The synthesis of the amide starting materials **4** and **6** for this investigation is shown in Scheme 1. The reaction of the acid chloride **2** (prepared from the 2-iodo benzoic acid with the oxalyl chloride in dichloromethane in the presence of a catalytic amount of DMF) with **3** and/or **5** in DCM–triethylamine in the presence of a catalytic amount of DMAP at rt for 2 h gave the corresponding amide precursors[29] **4(a–c)** and **6(a–c)**.

Based on the precedence of one generalized intramolecular reaction that has been used for the synthesis of heterocyclic compounds by treatment with tributyltin hydride in the presence of AIBN[30] as radical initiator, we decided to carry out the cyclization via this established protocol. However, only the reductive deiodination product was obtained under these and related conditions rather than the desired cyclized amide product. These negative results led us to explore an intramolecular palladium-catalyzed cyclization. When the Heck reaction was performed[31] with **4a** as amide precursor in the presence of $Pd(OAc)_2$ as the catalyst and anhydrous potassium acetate as a base, tetrabutylammonium bromide (TBAB) as additive in dry DMF under a nitrogen atmosphere for 10 h, the cyclized amide product **7a** was obtained in 91% yield. The optimum conditions for the cyclization were found through a series of experiments where sequential changes were made to the catalyst, base, ligand and solvent used (Table 1). We found that the catalysts and ligands have a profound effect on the reaction yield. The catalyst, $Pd(OAc)_2$, which is mostly used in this type of cyclization reaction, provided a 91% yield of product **7a**, whereas $PdCl_2$ provided **7a** in 51% yield. The ligand triphenylphosphine (entries 5 and 6) also proved to be effective in this case and gave 68% and 31% yield using $Pd(OAc)_2$ and $PdCl_2$ as the catalysts, respectively. However, these catalytic systems were not so effective as $Pd(OAc)_2$ or $PdCl_2$ (entries 3 and 4). With $Pd(OAc)_2/Ag_2CO_3/PPh_3$ and $PdCl_2/Ag_2CO_3/PPh_3$, the reaction was extremely slow and afforded **7a** in 39% and 27%, respectively, with unreacted starting material, **4a**, remaining even after 72 h.

Table 1
Palladium-catalyzed cyclization[a] of **4a** to **7a**

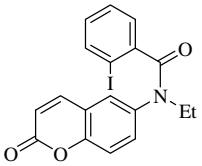
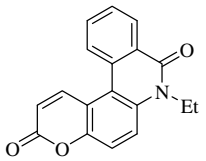
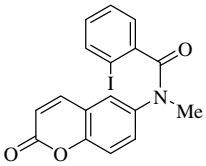
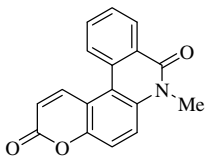
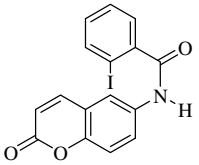
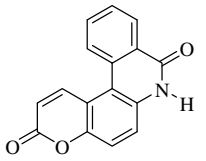
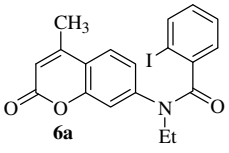
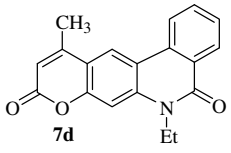
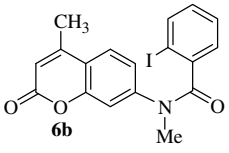
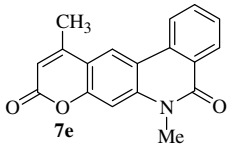
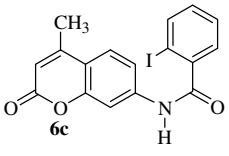
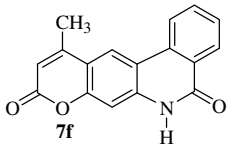


4a **7a**

Entry	Catalyst[b]	Base[c]	Ligand[d]	Additive[e]	Solvent	Yield[f] (%)
1	$Pd(OAc)_2$	KOAc	—	TBAB	DMF	91
2	$PdCl_2$	KOAc	—	TBAB	DMF	51
3	$Pd(OAc)_2$	Et_3N	—	TBAB	DMF	78
4	$PdCl_2$	Et_3N	—	TBAB	DMF	40
5	$Pd(OAc)_2$	Et_3N	PPh_3	—	DMF	68
6	$PdCl_2$	Et_3N	PPh_3	—	DMF	31
7	$PdCl_2$	Ag_2CO_3	PPh_3	—	DMF	39
8	$Pd(OAc)_2$	Ag_2CO_3	PPh_3	—	DMF	27
9	$PdCl_2$	Ag_2CO_3	—	TBAB	DMF	34
10	$PdCl_2$	KOAc	PPh_3	TBAB	CH_3CN	0
11	$PdCl_2$	KOAc	PPh_3	TBAB	Dioxane	0
12	$Pd(OAc)_2$	Ag_2CO_3	PPh_3	—	CH_3CN	0

[a] All reactions were carried out at 120 °C for 10 h.
[b] Catalyst used in the reaction 10 mol %.
[c] KOAc and Et_3N used in the reaction is 1.2 equiv, Ag_2CO_3 used in the reaction is 2 equiv.
[d] 20 mol % ligand used in the reaction.
[e] The additive used in each case in the reaction is 2.75 equiv.
[f] Isolated yields.

Table 2
Summarized results of the amide cyclization[a] by Pd-catalyzed Heck reaction

Entry	Amide precursors	Product	Yield[b] (%)
1	 **4a**	 **7a**	91
2	 **4b**	 **7b**	88
3[c]	 **4c**	 **7c**	59
4	 **6a**	 **7d**	84
5	 **6b**	 **7e**	82
6[c]	 **6c**	 **7f**	61

[a] All reactions were performed at optimized conditions except **4c** and **6c**.
[b] Isolated yields.
[c] Compounds **4c** and **6c** underwent cyclization at 160 °C using Ag_2CO_3 as the base.

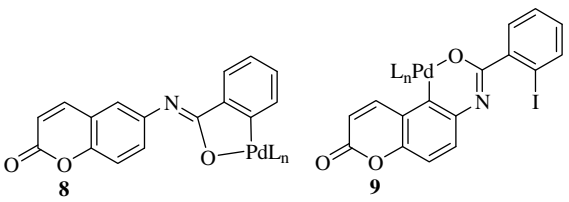


Fig. 1.

The effect of base on the reaction was also investigated. With KOAc as the base the reaction was over in 10 h (entry 1). The replacement of KOAc with an organic base such as Et_3N was found to be less effective. Other bases that have been explored include Ag_2CO_3 though this was not as effective as KOAc except in the case of **4a** and **6c**.

A study of the influence of various solvents (DMF, CH_3CN and dioxane) suggested that DMF is the best choice. No reaction was found to occur at 80 °C or at lower temperatures. To examine the versatility of this intramolecular palladium-catalyzed cyclization, a number of amino coumarin-annulated cyclic amide derivatives were synthesized by employing the optimized reaction condition, $Pd(OAc)_2$/KOAc/TBAB/DMF. The results are summarized in Table 2.

Here it is important to note that under these optimized conditions the free amides **4c** and **6c** did not undergo cyclization perhaps due to the low reactivity of the palladium(II) complexes **8** and **9** (which are likely to be formed in the presence of a base) to undergo the reaction. However, at elevated temperature (160 °C) and in the presence of the base Ag_2CO_3 (4 equiv) the reaction gave the desired cyclized products **7c** and **7f**, respectively (Fig. 1).

In conclusion, we have developed a convenient and high yielding method for the synthesis of cyclic amide derivatives by the intramolecular Heck cyclization starting from the secondary amide and N-alkylated tertiary amide precursors. This method is new and highly efficient for the cyclization of the biaryl systems and is found to be a straightforward approach, whereas the radical mediated cyclization protocol failed to afford any cyclized product.

Acknowledgements

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29. *General procedure for the preparation of the amide precursors*:
DMAP (5 mg) and Et_3N (2 ml) were added to a dry dichloromethane solution of **3a** (300 mg, 1.6 mmol) at ice-bath temperature. 2-Iodobenzoyl chloride (prepared from 2-iodobenzoic acid and oxalyl chloride) in dry dichloromethane solution (10 ml) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature. The mixture was then washed with water (3 × 15 ml) and brine (20 ml) and dried (Na_2SO_4). Evaporation of the DCM gave a crude mass which was purified by chromatography by 40% ethyl acetate–pet. ether to afford product **4a**. Compounds **4(b,c)** and **6(a–c)** were obtained by the same procedure.
Compound **4a**: Yield: 84%; solid; mp 120–122 °C. IR. (KBr): $\nu_{max} = 1650, 1732\ cm^{-1}$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 1.27$ (t, 3H, $J = 7.1$ Hz, CH_2–CH_3), 3.98 (q, 2H, $J = 7.1$ Hz, N–CH_2), 6.39 (d, 1H, $J = 9.6$ Hz, C_3–*H* of coumarin), 6.84 (t, 1H, $J = 7.2$ Hz, Ar*H*), 7.01 (d, 1H, J = 7.2 Hz, Ar*H*), 7.11–7.22 (m, 2H, Ar*H*), 7.33–7.34 (m, 2H, Ar*H*), 7.44 (d, 1H, $J = 8.99$ Hz, Ar*H*), 7.53 (d, 1H, $J = 9.6$ Hz, C_4–*H* of coumarin). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 7.9, 39.5, 88.5, 112.5, 112.6, 113.9, 122.1, 122.6, 123.2, 125.0, 126.6, 132.9, 134.3, 137.0, 137.4, 147.6, 154.9, 159.3. MS: $m/z = 419$ [M^+]. Anal Calcd for $C_{18}H_{14}INO_3$: C, 51.57; H, 3.37; N, 3.34. Found: C, 51.59; H, 3.41; N, 3.27%.
Compound **4c**: Yield: 81%; solid; mp 210–212 °C. IR (KBr): $\nu_{max} = 1660,\ 1712,\ 3332\ cm^{-1}$. ^{1}HNMR (DMSO-$d_6$, 400 MHz):

$\delta_H = 6.51$ (d, 1H, $J = 9.6$ Hz, C_3–*H* of coumarin), 6.95–6.99 (m, 2H, Ar*H*), 7.43 (dd, 2H, $J = 8.9$ Hz, $J = 2.4$ Hz, Ar*H*), 7.82 (dd, 1H, $J = 8.9$ Hz, $J = 2.4$ Hz, Ar*H*), 7.95 (dd, 1H, $J = 7.8$ Hz, $J = 1.2$ Hz, Ar*H*), 8.11 (d, 1H, $J = 9.6$ Hz, C_4–*H* of coumarin), 8.16 (d, 1H, $J = 2.4$ Hz, Ar*H*), 10.58 (s, 1H, N*H*). MS: $m/z = 391$ [M^+]. Anal. Calcd for $C_{16}H_{10}INO_3$: C, 49.13; H, 2.58; N, 3.58. Found: C, 49.19; H, 2.43; N, 3.61.

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31. *General procedure for the intramolecular Heck cyclization*:
A mixture of compound **4a** (100 mg, 0.23 mmol), anhydrous potassium acetate (28 mg, 0.28 mmol), tetrabutylammonium bromide (211 mg, 0.65 mmol) and $Pd(OAc)_2$ (5.3 mg, 10 mol %) was heated in dry DMF under nitrogen atmosphere at 120 °C for 10 h with continuous stirring. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and water was added (3 ml). It was extracted with ethyl acetate (3 × 25 ml) and washed with water (3 × 15 ml) followed by brine (20 ml). The organic layer was dried (Na_2SO_4). Evaporation of ethyl acetate furnished the crude mass, which was purified by column chromatography over silica-gel. Elution of the column with 30% ethyl acetate–pet. ether afforded product **7a**. Similarly the other substrates **4b** and **6(a,b)** were subjected to the reaction under the same conditions to give products **7(b,d,e)**.

The preparation of compounds **7c** and **7f** are by the same procedure except that the reagents used were Ag_2CO_3 (4 equiv), catalyst $Pd(OAc)_2$ (20 mol %), ligand PPh_3 (40 mol %) and solvent DMF at 160 °C for 10 h.

Compound **7a**: Yield: 91%; solid; mp 200–202 °C. IR (KBr): $\nu_{max} = 1650$, 1727 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 1.42$ (t, 3H, $J = 6.9$ Hz, CH_2–CH_3), 4.47 (q, 2H, $J = 6.9$ Hz, N–CH_2), 6.55 (d, 1H, $J = 10.0$ Hz, C_3–*H* of coumarin), 7.53 (d, 1H, $J = 9.3$ Hz, Ar*H*), 7.62 (d, 1H, $J = 9.3$ Hz, Ar*H*), 7.68 (t, 1H, $J = 7.2$ Hz, Ar*H*), 7.80 (t, 1H, $J = 7.7$ Hz, Ar*H*), 8.08 (d, 1H, $J = 10.0$ Hz, C_4–*H* of coumarin), 8.61 (d, 2H, $J = 9.9$ Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 7.9, 33.2, 110.5, 111.5, 112.2, 113.1, 113.5, 121.9, 122.7, 123.9, 124.3, 126.9, 128.8, 129.2, 136.9, 146.1, 156.2, 158.5. HRMS: calcd for $C_{18}H_{13}NO_3$: 292.0895 [M+H]; found: 292.0899 [M+H]. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.29; H, 4.44; N, 4.99.

Compound **7c**: Yield: 59%; solid; mp 140–142 °C. IR (KBr): $\nu_{max} = 1665$, 1714 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 6.44 (d, 1H, $J = 9.5$ Hz, C_3–*H* of coumarin), 7.03 (d, 1H, $J = 8.3$ Hz, Ar*H*), 7.13 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.31 (d, 1H, $J = 8.8$ Hz, Ar*H*), 7.40 (dd, 1H, $J = 8.9$ Hz, $J = 2.4$ Hz, Ar*H*), 7.51 (m, 1H, Ar*H*), 7.72 (d, 1H, $J = 9.5$ Hz, C_4–*H* of coumarin), 8.27–8.30 (m, 1H, Ar*H*), 10.19 (s, 1H, N*H*). MS: $m/z = 263$ [M^+]. Anal. Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 73.09; H, 3.61; N, 5.21.