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Synthesis of Pyridocoumarin derivative by arylation of tertiary and secondary amide via Palladium catalyzed intramolecular cyclization

*Sanjay Nath
Department of Chemistry, Krishnath College, Berhampore, Murshidabad, W.B., India
Corresponding Author: Sanjay Nath

***Abstract**: A synthetic protocol has been developed for the arylation of N-alkylated tertiary amide and secondary amide as Heck precursors by the implementation of the palladium-catalyzed intramolecular Heck reaction strategies and by this methodology pyridocoumarin derivative have been synthesized.*

***Keywords**: 7- Amino coumarin. Biaryl coupling, Heck reaction, Intramolecular cyclization, Palladium catalysts, Pyridocoumarin.*

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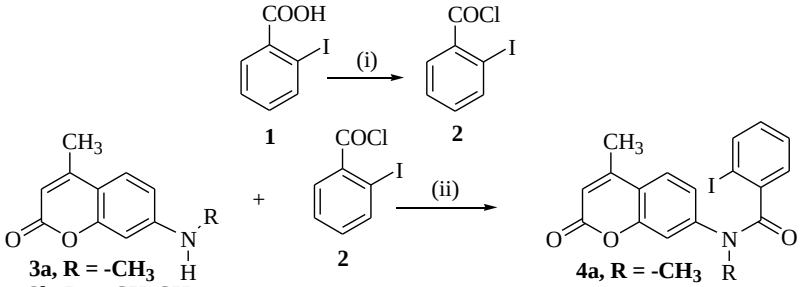
I. Introduction

The search of new methodology for the construction of organic molecules particularly heterocyclic compounds 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 synthetic protocol developed for the synthesize of condensed heteroaromatic compounds using biaryl coupling reactions with palladium reagents [7-11] by the regioselective C-H bond activation using the intramolecular coordination of the amine to palladium [12-15]. It had been reported [16, 17] 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. Trauner *et al* reported [18] 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 et al [19] tried the direct palladium-catalyzed intramolecular cyclization with the secondary amide; but their all 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 et al [20] tried the reaction and their attempts of Heck reaction of free amide or N-methyl derivatives of the secondary amide led to low yield of the cyclized product (15-17% yield). Then we have developed [21] a high yielding method for the synthesis of pyridocoumarin derivative by the application of intramolecular Heck reaction starting from secondary and tertiary amide. But that methodology requires harsh reaction condition. Therefore, the above-mentioned findings have prompted me 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 compound, pyridocoumarin derivatives in a relatively convenient way.

Further additional interest is derived from the synthesis of coumarin-annulated heterocyclic compounds, as coumarins fused with heterocycles and aza-analogues of coumarins have received increasing attention due to their potential biological activities [22-24]. In particular, those coumarins fused to pyridines have been reported to possess antiallergic, [25] antidiabetic,[26] and analgesic [27] properties. Here I have undertaken a study for the synthesis of pyridocoumarin derivative by the application of intramolecular Heck reaction with amide as Heck precursor. This methodology is attractive from the synthetic point of view due to high chemoselectivity and mild reaction conditions associated with low toxicity and cost of the reagents as it require only in catalytic amount [28].

II. Result And Discussion

The synthesis of the amide starting materials **4** to be used in the investigation of the palladium-catalyzed intramolecular Heck cyclization is shown in **Scheme 1**. First the acid chloride **2** was prepared from the reaction of 2-iodo benzoic acid **1** with the oxalyl chloride in dichloromethane solution in the presence of a catalytic amount of DMF. The reaction of the acid chloride **2** with *N*- substituted 4-methyl 7- amino coumarin derivatives **3a-g** in DCM and triethylamine in the presence of a catalytic amount of DMAP at rt for 2 h gave the corresponding amide Heck precursors **4a-g**.



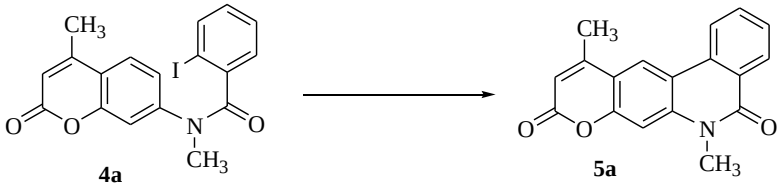
3a, R = -CH$_3$
3b, R = -CH$_2$CH$_3$
3c, R = -CH$_2$CH$_2$CH$_3$
3d, R = -CH(CH$_3$)$_2$
3e, R = -(CH$_2$)$_3$CH$_3$
3f, R = -(CH$_2$)$_4$CH$_3$
3g, R = H

4a, R = -CH$_3$
4b, R = -CH$_2$CH$_3$
4c, R = -CH$_2$CH$_2$CH$_3$
4d, R = -CH(CH$_3$)$_2$
4e, R = -(CH$_2$)$_3$CH$_3$
4f, R = -(CH$_2$)$_4$CH$_3$
4g, R = H

Scheme 1. Reagent and condition: (i) DCM, DMF, $(COCl)_2$, 0^0C, 30 min;
(ii) DCM, Et_3N, DMAP, rt, 2h

When the Heck reaction was performed with **4a** as amide precursor in the presence of the catalyst $Pd(OAc)_2$ (10 mol%) and cesium carbonate as a base (1 eqv.), tetrabutylammonium bromide (TBAB) as additive (20 mol%) in dry DMF under nitrogen atmosphere for 6 h, at 95^0C the cyclized amide product **5a** obtained in 91% yield. The optimum condition for the cyclization was found through a series of experiments where sequential changes were made to the catalyst, base, ligand and solvent used (**Table 1**).

Table 1. Palladium-Catalyzed Cyclization[a] of **4a** to **5a**



4a **5a**

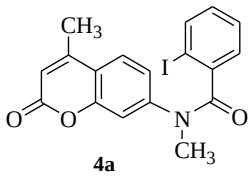
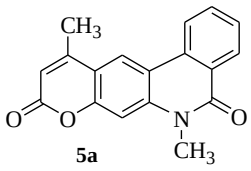
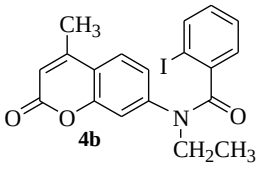
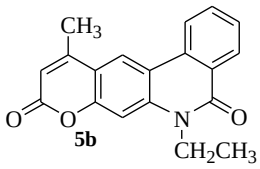
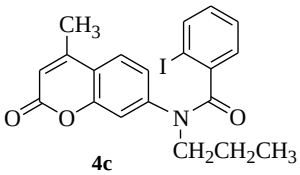
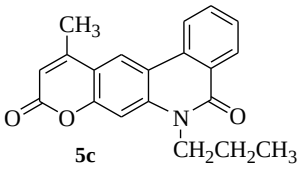
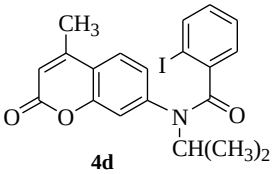
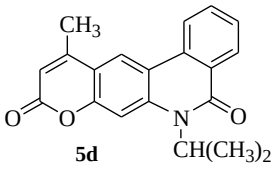
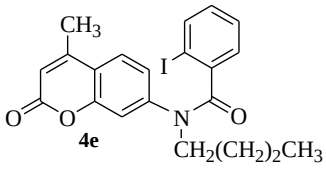
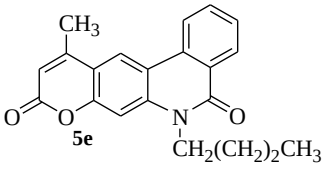
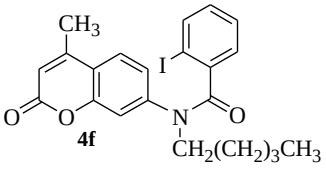
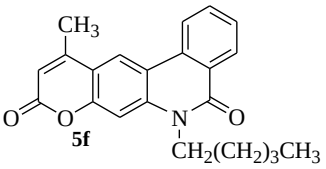
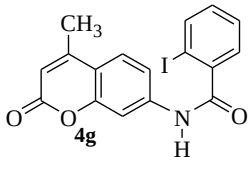
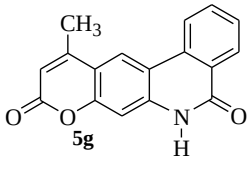
Entry	Catalyst[b]	Base[c]	Ligand[d]	Additive[e]	Solvent	Yield(%)[f]
1	$Pd(OAc)_2$	Cs_2CO_3	....	TBAB	DMF	90
2	$PdCl_2$	Cs_2CO_3	....		DMF	50
3	$Pd(OAc)_2$	Et_3N	....	TBAB	DMF	20
4	$PdCl_2$	Et_3N	....	TBAB	DMF	10
5	$Pd(OAc)_2$	Et_3N	PPh_3	.....	DMF	15
6	$PdCl_2$	Et_3N	PPh_3	.....	DMF	12
7	$PdCl_2$	Ag_2CO_3	PPh_3	.....	DMF	20
8	$Pd(OAc)_2$	Ag_2CO_3	PPh_3	.....	DMF	20
9	$PdCl_2$	Ag_2CO_3	.....	TBAB	DMF	10
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 95^0C for 6h. [b] Catalyst used in the reaction 10 mol%.
[c] Cs_2CO_3 used as 1 eqv. and Et_3N used as 1.2 equiv, Ag_2CO_3 used in the reaction as 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.

We found that the catalysts and ligands had a profound effect on the reaction yield. The catalyst $Pd(OAc)_2$ which is mostly used in this type cyclization reaction, provided a 90% yield of the product **5a**, where as $PdCl_2$ provided **5a** in 50% yield. The ligand triphenylphosphine also proved to be ineffective in this case and gave 15% and 12% yield using $Pd(OAc)_2$ and $PdCl_2$ as the catalyst respectively in presence of base triethylamine at 95^OC temperature. Under the condition $Pd(OAc)_2/Ag_2CO_3/PPh_3$ and $PdCl_2/Ag_2CO_3/PPh_3$, the reaction was extremely slow and afforded only 20% of **5a** with the unreacted starting material **4a** remaining after 36h. The effect of base on the reaction was also investigated. The rate of the reaction was increased by

using the inorganic base Cs_2CO_3 (**entry 1**). The starting material was completely consumed in 6h at 95^OC. The replacement of Cs_2CO_3 with an organic base such as Et_3N was found to be less effective compared to the inorganic base (Cs_2CO_3). Other bases that have been explored include Ag_2CO_3 though this was not as effective as Cs_2CO_3. In this case it has to be mentioned[21] that use of base KOAc was found to be effective and give 82% yield, but requires 120^OC temperature for 10h. A study of the influence of the various solvents (DMF, CH_3CN, Dioxane) suggested that DMF was the best choice. No reaction was found at 70^0C or its lower temperature.

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

Entry	Amide Precursors	Product	Yield(%)[b]
1	 **4a**	 **5a**	90
2	 **4b**	 **5b**	92
3	 **4c**	 **5c**	90
4	 **4d**	 **5d**	88
5	 **4e**	 **5e**	85
6	 **4f**	 **5f**	90
7[c]	 **4g**	 **5g**	75

[a] All reactions were performed at optimized conditions except **4g**. [b] Isolated yields. [c] Compounds **4g** underwent cyclization at 120 ^OC temparature using silver carbonateand cesium carbonate as the base.

In the same way other pyridocoumarin derivatives **5b-5g** are synthesized starting from the Heck precursors **4b-4g** by employing the optimized reaction condition, $Pd(OAc)_2$/ Cs_2CO_3/TBAB/DMF. Among other substrates **4b-4f** undergo cyclization under the optimized reaction condition. However, **4g** undergo cyclization at elevated temperature (120^0C) and in presence of the base Ag_2CO_3 (2 equiv) and Cs_2CO_3 (2 equiv.). The results are summarized in **Table 2**.

Here it is important to note that under this optimized condition the free amides **4g** did not undergo cyclization and this might be due to the reluctance of the palladium (II) complexes **6** and **7** which can be expected to form in the presence of a base to undergo the reaction. However, at elevated temperature (120^0C) and in presence of bases Ag_2CO_3 (2 equiv) and Cs_2CO_3 (2 equiv.) the reaction gave the desired cyclized products **5g** (**Figure 1**).

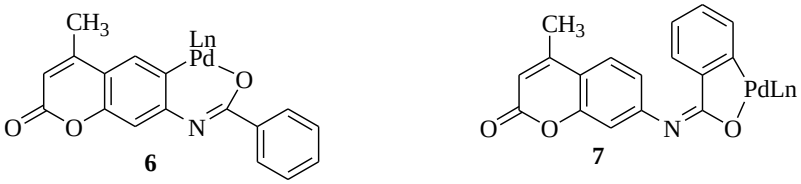


Figure 1.

III. Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded for KBr discs on a Perkin-Elmer 120-000A apparatus (ν_{max} in cm^{-1}) and NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard. Silica gel (60-120 mesh) was used for chromatographic separation. Silica gel-G [E-Mark (India)] was used for TLC. Petroleum-ether refers to the fraction between 60^0C and 80^0C.

III. 1 General procedure for the preparation of the amide precursors 4a-g:

To a dry dichloromethane solution of **3a** (300 mg, 1.6 mmol) DMAP (5 mg) and Et_3N (2 ml) were added at ice-bath temperature. 2-iodobenzoyl chloride **2** (prepared from 2-iodobenzoic acid and oxalyl chloride) in dry dichloromethane solution (10 ml) was added dropwise. The reaction mixture was stirred for 2h at the same temperature. The mixture was then washed with water (3 × 15 ml) and brine (20 ml) and dried over Na_2SO_4. Evaporation of the DCM gave a crude mass which was purified by chromatography by 40% ethylacetate-petether to afford the product **4a**. Compounds **4b-g** was obtained by the same procedure.

Compound 4a: Yield 79%, solid, m.p. 190-192^{0}C. IR(KBr): ν_{max} = 1649, 1733 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 2.36 (s, 3H, C**H$_3$**), 3.52 (s, 3H, N-C**H$_3$**), 6.23 (s, 1H, C_3-**H** of coumarin), 6.93 (m, 1H, Ar**H**), 7.10-7.21 (m, 3H, Ar**H**), 7.35-7.41 (m, 2H, Ar**H**), 7.68 (m, 1H, Ar**H**). 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, 51.69; H, 3.43; N, 3.29%.

Compound 4b: Yield 84%, solid, m.p. 155-157^{0}C. IR(KBr): ν_{max} = 1641, 1727 cm^{-1}. ^{1}H-NMR (d^{6}DMSO, 400 MHz): δ_H = 1.24 (t, 3H, *J* = 7.3 Hz, CH_2-C**H$_3$**), 2.36 (s, 3H, C**H$_3$**), 4.02 (q, 2H, *J* = 7.3 Hz, N-C**H$_2$**), 6.24 (s, 1H, C_3-**H** of coumarin), 6.88-6.95 (m, 1H, Ar**H**), 7.10-722 (m, 4H, Ar**H**), 7.40 (m, 1H, Ar**H**), 7.67 (m, 1H, Ar**H**). MS (m/z): 433 (M^+). Anal. Calcd. for $C_{19}H_{16}INO_3$: C, 52.67; H, 3.72; N, 3.23%. Found: C, 52.79; H, 3.88; N, 3.20%.

Compound 4c: Yield 92%, solid, m.p. 165-167^{0}C. IR: (KBr): ν_{max} = 1650, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.12 (t, 3H, J = 7.4 Hz, -NCH_2CH_2C**H$_3$**), 1.35-1.46 (m, 2H, -NCH_2C**H$_2$**CH_3), 2.38 (s, 3H, C**H$_3$**), 3.80 (t, 2H, J = 7.8 Hz, -NC**H$_2$**CH_2CH_3), 6.20 (s, 1H, C_3-**H** of coumarin), 6.90-6.98 (m, 2H, Ar**H**), 7.12 (d, 1H, J =7.0 Hz, Ar**H**), 7.25-7.29 (m, 3H, Ar**H**), 7.65-7.70 (m, 1H, Ar**H)**. MS (*m/z*): 447 (M^+). Anal Calcd. for $C_{20}H_{18}INO_3$: C, 53.71; H, 4.06; N, 3.13%. Found: C, 53.75; H, 4.01; N, 3.16%.

Compound 4d: Yield 80%, solid, m.p. 118-120^{0}C. IR. (KBr): ν_{max} = 1665, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.46 (d, 6H, J = 7.3 Hz, -NCH(C**H$_3$**)$_2$), 2.37 (s, 3H, C**H$_3$**), 3.76-3.82 (m, 1H, NC**H(**CH_3)$_2$), 6.31 (s, 1H, C_3-**H** of coumarin), 7.12-7.18 (m, 1H, Ar**H**), 7.52-7.59 (m, 4H, Ar**H**), 7.69 (t, 2H, *J* = 8.7 Hz, Ar**H**). MS (*m/z*): 447 (M^+). Anal Calcd. for $C_{20}H_{18}INO_3$: C, 53.71; H, 4.06; N, 3.13%. Found: C, 53.65; H, 4.10; N, 3.18%.

Compound 4e: Yield 93%, solid, m.p. 145-147^{0}C. IR. (KBr): ν_{max} = 1655, 1747 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 0.98 (t, 3H, J = 7.2 Hz, -$NCH_2CH_2CH_2C$**H$_3$**), 1.25 (m, 2H, -NCH_2CH_2C**H$_2$**CH_3), 1.72 (m, 2H, -NCH_2C**H$_2$**CH_2CH_3), 2.36 (s, 3H, C**H$_3$**), 3.62 (t, 2H, J = 7.8 Hz, -NC**H$_2$**$CH_2CH_2CH_3$), 6.39 (s, 1H, C_3-**H** of coumarin), 6.82 (d, 1H, *J* = 7.2 Hz, Ar**H**), 7.24 (d, 1H, J =7.2 Hz, Ar**H**), 7.34-7.39 (m, 1H, Ar**H**), 7.48-7.53 (m, 2H, Ar**H**), 7.60-7.68 (m, 2H, Ar**H**). MS (*m/z*): 447 (M^+). Anal Calcd. for $C_{21}H_{20}INO_3$: C, 54.68; H, 4.37; N, 3.04%. Found: C, 54.75; H, 4.45; N, 2.98%.

Compound 4f: Yield 80%, solid, m.p. 156-158^{0}C. IR. (KBr): ν_{max} = 1651, 1736 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 0.92 (t, 3H, J = 6.7 Hz, -$NCH_2CH_2CH_2CH_2C$**H$_3$**), 1.32-1.36 (m, 4H, -NCH_2CH_2C**H$_2$**C**H$_2$**CH_3), 1.70 (quintet, 2H, J = 7.2 Hz, -NCH_2C**H$_2$**$CH_2CH_2CH_3$), 2.34 (s, 3H, C**H$_3$**), 3.55 (t, 2H, J = 7.2 Hz, -NC**H$_2$**$CH_2CH_2H_2CH_3$), 6. 40 (s, 1H, C_3-**H** of coumarin), 6.54-6.58 (m, 2H, Ar**H**), 6.82 (d, 1H, J =7.4 Hz, Ar**H**), 7.40-7.44 (m, 2H, Ar**H**), 7.62-7.67 (m, 2H, Ar**H)**. MS (*m/z*): 475 (M^+). Anal Calcd. for $C_{22}H_{22}INO_3$: C, 55.59; H, 4.67; N, 2.95%. Found: C, 55.50; H, 4.72; N, 3.10%.

Compound 4g: Yield 85%, solid, m.p. 180-182^{0}C. IR(KBr): ν_{max} = 1660, 1690 cm^{-1}. ^{1}H-NMR (d^{6}DMSO, 400 MHz): δ_H = 2.32 (s, 3H, C**H$_3$**), 6.30 (s, 1H, C_3-**H** of coumarin), 7.26 (q, 1H, *J* = 4.5 Hz, Ar**H**), 7.52 (d, 2H, *J* =

4.2 Hz, Ar**H**), 7.65 (d, 1H, *J* = 8.8 Hz, Ar**H**), 7.77 (d, 1H, *J* = 8.7 Hz, Ar**H**), 7.83 (s, 1H, Ar**H**), 7.96 (d, 1H, *J* = 7.9 Hz, Ar**H**), 10.85 (s, 1H, N**H**). MS (*m/z*): 405 (M^+). Anal. Calcd. for $C_{17}H_{12}INO_3$: C, 50.39; H, 2.99; N, 3.46%. Found: C, 50.51; H, 3.09; N, 3.39%.

III. 2 General procedure for the intramolecular Heck cyclization:

A mixture of compound **4a** (100 mg, 0.23 mmol), cesium carbonate (75 mg, 0.23 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 95^OC for 6h 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 x 25 ml) and washed with water (3 x 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-petether afforded the product **5a**. Similarly the other substrates **4b-f** were subjected to the reaction under the same conditions to give products **5b-f**. The preparation of the compounds **5g** are the same; only differences are that the reagents used is Ag_2CO_3 (2 equiv), Cs_2CO_3 (2 equiv.) catalyst $Pd(OAc)_2$ (20 mol%), ligand PPh_3 (40 mol%), solvent DMF at 120^OC for 6h.

Compound 5a: Yield 90%, solid, m.p. 290-292^{0}C. IR(KBr): ν_{max} = 1650, 1736 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 2.52 (s, 3H, C**H$_3$**), 3.48 (s, 3H, N-C**H$_3$**), 6.31 (s, 1H, C_3-**H** of coumarin), 7.31 (s, 1H, C_5-**H** of coumarin), 7.63 (t, 1H, *J* = 7.3 Hz, Ar**H**), 7.78-7.80 (m, 1H, Ar**H**), 8.26 (d, 1H, *J* = 8.2 Hz, Ar**H**), 8.43 (s, 1H, C_8-**H** of coumarin), 8.53 (dd, 1H, *J* = 7.9 Hz, J = 1.1 Hz, Ar**H**). MS (*m/z*): 291 (M^+). Anal. Calcd. for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81%. Found: C, 74.19; H, 4.53; N, 4.74%.

Compound 5b: Yield 92%, solid, m.p. 215-217^{0}C. IR(KBr): ν_{max} = 1646, 1729 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.41 (t, 3H, *J* = 7.1 Hz, CH_2-C**H$_3$**), 2.52 (s, 3H, C**H$_3$**), 4.52 (q, 2H, *J* = 7.1 Hz, N-C**H$_2$**), 6.31 (s, 1H, C_3-**H** of coumarin), 7.33 (s, 1H, C_5-**H** of coumarin), 7.42 (d, 1H, *J* = 9.0 Hz, Ar**H**), 7.65 (t, 1H, *J* = 7.7 Hz, Ar**H**), 7.76 (d, 1H, *J* = 9.0 Hz, Ar**H**), 7.88 (t, 1H, *J* = 7.2 Hz, Ar**H**), 8.54 (s, 1H, C_8-**H** of coumarin). MS (*m/z*): 305 (M^+). Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59%. Found: C, 74.87; H, 5.03; N, 4.47%.

Compound 5c: Yield 90%, solid, m.p 210-212°C. IR (KBr): ν_{max} = 1645, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.04 (t, 3H, J = 7.4 Hz, -NCH_2CH_2C**H$_3$**), 1.55 (m, 2H, CH_2C**H$_2$**CH_3), 2.50 (s, 3H, C**H$_3$**), 4.45 (t, 2H, *J* = 7.5 Hz, N-C**H$_2$**CH_2CH_3), 6.35 (s, 1H, C_3-**H** of coumarin), 7.39 (s, 1H, C_5-**H** of coumarin), 7.45 (d, 1H, *J* = 9.0 Hz, Ar**H**), 7.76 (t, 1H, *J* = 7.7 Hz, Ar**H**), 7.81 (d, 1H, *J* = 9.0 Hz, Ar**H**), 7.92 (t, 1H, *J* = 7.2 Hz, Ar**H**), 8.46 (s, 1H, C_8-**H** of coumarin). MS (*m/z*): 319 (M^+). Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39 %. Found: C, 75.26; H, 5.34; N, 4.44 %.

Compound 5d: Yield 88%, solid, m.p 200-202°C. IR (KBr): ν_{max} = 1652, 1733 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.71 (d, 6H, J = 7.5 Hz, -NCH(C**H$_3$**)$_2$), 2.50 (s, 3H, C**H$_3$**), 4.12 (m, 1H, NC**H**$(CH_3)_2$), 6.33 (s, 1H, C_3-**H** of coumarin), 7.42 (s, 1H, C_5-**H** of coumarin), 7.70 (t, 1H, *J* = 7.3 Hz, Ar**H**), 7.92-7.99 (m, 1H, Ar**H**), 8.32 (d, 1H, *J* = 8.2 Hz, Ar**H**), 8.45 (dd, 1H, *J* = 7.4 Hz, J = 1.6 Hz, Ar**H**), 8.52 (s, 1H, C_8-**H** of coumarin). MS (*m/z*): 319 (M^+). Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39 %. Found: C, 75.18; H, 5.41; N, 4.43 %.

Compound 5e: Yield 85%, solid, m.p 178-180^{O}C. IR (KBr): ν_{max} = 1654, 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 1.10 (t, 3H, J = 7.0 Hz, -$NCH_2CH_2CH_2C$**H$_3$**), 1.30-1.36 (m, 2H, -NCH_2CH_2C**H$_2$**CH_3), 1.62-1.68 (m, 2H, -NCH_2C**H$_2$**CH_2CH_3), 2.50 (s, 3H, C**H$_3$**), 4.06 (t, 2H, J = 7.8 Hz, -NC**H$_2$**$CH_2CH_2CH_3$), 6.31 (s, 1H, C_3-**H** of coumarin), 7.40 (s, 1H, C_5-**H** of coumarin), 7.55 (d, 1H, *J* = 8.5 Hz, Ar**H**), 7.65-7.71 (m, 1H, Ar**H**), 7.81 (dd, 1H, *J* = 8.5 Hz, *J* = 2.1 Hz, Ar**H**), 7.92 (t, 1H, *J* = 7.2 Hz, Ar**H**), 8.55 (s, 1H, C_8-**H** of coumarin). MS (*m/z*): 333 (M^+). Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20 %. Found: C, 75.70; H, 5.70; N, 4.25 %.

Compound 5f: Yield: 90 %, Yellow solid, mp. 205 - 207^{o}C. IR(KBr): ν_{max} = 1625, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H = 0.96 (t, 3H, J = 6.4 Hz, -$NCH_2CH_2CH_2CH_2C$**H$_3$**), 1.34-1.40 (m, 4H, -NCH_2CH_2C**H$_2$**C**H$_2$**CH_3), 1.81 (quintet, 2H, J = 7.2 Hz, -NCH_2C**H$_2$**$CH_2CH_2CH_3$), 2.52 (s, 3H, C**H$_3$**), 4.45 (t, 2H, J = 7.2 Hz, -NC**H$_2$**$CH_2CH_2H_2CH_3$), 6.35 (s, 1H, C_3-**H** of coumarin), 7.26 (s, 1H, C_5-**H** of coumarin), 7.47 (d, 1H, *J* = 9.2 Hz, Ar**H**), 7.74 (t, 1H, *J* = 7.5 Hz, Ar**H**), 7.89 (d, 1H, *J* = 9.2 Hz, Ar**H**), 7.99 (t, 1H, *J* = 7.2 Hz, Ar**H**), 8.54 (s, 1H, C_8-**H** of coumarin). MS: m/z = 347 [M^+]. Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03 %. Found: C, 76.15; H, 6.15; N, 3.98 %.

Compound 5g: Yield 75%, solid, m.p. 245-247^{0}C. IR (KBr): ν_{max} = 1671, 1689, 3336 cm^{-1}. ^{1}H-NMR (d^{6}DMSO, 400 MHz): 2.52 (s, 3H, C**H$_3$**), 6.29 (s, 1H, C_3-**H** of coumarin), 7.56 (t, 1H, *J* = 7.2 Hz, Ar**H**), 7.62 (d, 1H, *J* = 7.2 Hz, Ar**H**), 7.77 (s, 2H, C_5-**H** and C_8-**H** of coumarin), 7.95-7.99 (m, 2H, Ar**H**), 10.64 (s, 1H, N**H**). MS (*m/z*): 277 (M^+). Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05%. Found: C, 73.80; H, 4.11; N, 5.13%.

IV. Conclusion

In conclusion, pyridocoumarin derivative have been synthesized by a convenient and high yielding method by the intramolecular Heck cyclization starting from the secondary amide and N-alkylated tertiary amide Heck precursors. This method is highly efficient for the cyclization of the biaryl systems and synthesis of pyridocoumarin derivative.

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