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Effectual Direct Synthesis of Diversely Substituted 4-aryl/alkyl Coumarins by Palladium Catalyzed Oxidative Suzuki–Miyaura Coupling

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ABSTRACT

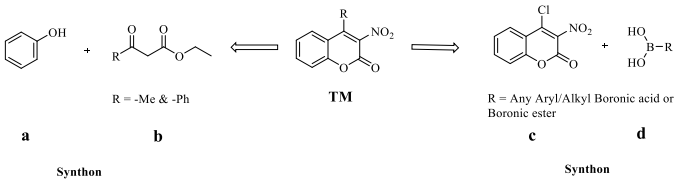
An effectual direct synthesis of 4-aryl/alkyl substituted coumarin was developed using a palladium-catalyzed oxidative Suzuki–Miyaura coupling reaction strategy. Use of $Pd_2(dba)_3$ in the presence of Na_2CO_3 in THF solvent was found to be the most effective reaction condition for excellent yield.

Keywords: 4-aryl/alkylcoumarins, Suzuki-Miyaura coupling, Palladium catalyst, Boronic acid or ester

I. INTRODUCTION

4-arylcoumarins as the family members of flavonoids are broadly occurs in natural products such as Asteraceae, Clusiaceae, Fabaceae, Loraceae, Passif, Rubiaceae, Rutaceae, and Thelypteridaceae.[1] Besides, they exhibit several important biological activities [1,2] such as antitumor,[3] antimalarial, [4] cytotoxic,[5] antibacterial,[6] anti-inflammatory,[7] anti-HIV,[8] antiprotozoal,[9] antidiabetic,[10] and antivirus properties.[11] Without a doubt, many future pharmaceutical applications will require the development of 4-arylcoumarins to fulfill the increasing demand and practical requirements.

The general methods for the preparation of 4-arylcoumarins involves the reaction between different phenol with various β-keto ester in the presence of acidic catalysts such as polyphosphoric acid (PPA),[12] $InCl_3$,[13] $ZrCl_4$,[14] $Yb(OTf)_3$,[15–18] p-TsOH,[19] $BiCl_3$,[20] or AgOTf,[21] and $Sm(NO_3)_3$,[22] as well as chloroaluminate ionic liquids.[23,24] The main drawbacks of the processes using these catalysts are longer reaction time, large amount of the catalyst, and boring purification process after completion of the reaction. Some of the existing methods degrade the catalysts in the workup procedure and they cannot be recovered. Limitation of this method are synthesized only several compounds regarding varieties of phenol(**a**) and β-keto ester(**b**),[25] shown in scheme-1.

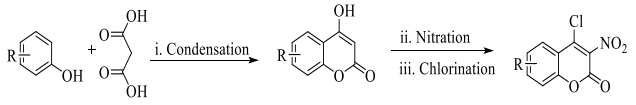


Scheme 1

As per scheme -1 if we disconnect our target molecule (**TM)** we got phenol(**a**) and β-keto ester(**b**) as a synthon. There is limited substitution of β-keto ester, so we synthesize limited number of TM. However, these routes suffer from poor atom-economic, stoichiometric amounts of mineral or Lewis acids, toxic reagents, and poor yields but in another route 4-choloro coumarin(**c**) and various boronic acid (**d**) as synthon. Here we are synthesize number of 4-alkyl/aryl coumarin using various type of boronic acid or ester with 4-chloro-coumarin and $Pd_2(dba)_3$ in the presence of Na_2CO_3 in THF solvent was found to be the most effective reaction condition for excellent yield.

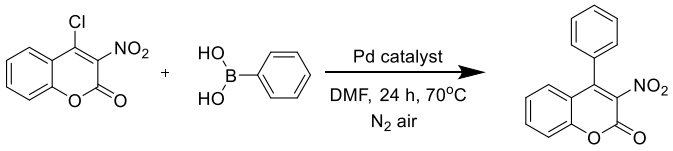
II. Result and Discussion

The reaction of malonic acid with substituted phenols in presence of strong acid was afforded 4-hydroxy coumarin derivatives in good yields. The reaction of 4-hydroxy coumarin with Nitric acid introduced -NO_2 group at 3rd position. These coumarin derivatives on reaction with $SOCl_2$ or $POCl_3$ in presence of base were furnished 4-chloro 3-nitro coumarin, shown in scheme-2.



Scheme 2

To establish efficient cross-coupling conditions, coumarin and phenylboronic acid (scheme-3) were selected as the model to screen the reaction parameters (Table-1). Our initial experiments showed that $Pd_2(dba)_3$/DMF as catalytic system was able to give the coupling product in 82% (Table-1, entry 4). However, no coupling product was detected in the case of $Pd(PPh_3)_4$ as catalyst (Table-1, entry 13). Next, various catalyst and base were investigated in order to find the most efficient one (Table-1).

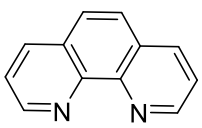


Scheme 3

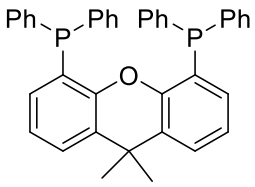
Table 1: Optimized Conditions for the Synthesis of 3-nitro 4- Phenylcoumarins

Entry	Catalyst	ligand	Base	% of Yield[a]
1	$Pd(OAc)_2$	L1	Cs_2CO_3	60
2	$Pd(OAc)_2$	L2	Cs_2CO_3	30
3	$Pd(OAc)_2$	L3	Cs_2CO_3	25
4[b]	**$Pd_2(dba)_3$**	**-**	**Na_2CO_3**	**82**
5	$Pd_2(dba)_3$	-	K_2CO_3	70
6	$Pd_2(dba)_3$	-	Cs_2CO_3	60
7	$Pd(OAc)_2$	L1	K_2CO_3	62
8	$Pd(OAc)_2$	L2	K_2CO_3	38
9	$Pd(OAc)_2$	L3	K_2CO_3	32
10	$Pd(OAc)_2$	L1	Na_2CO_3	65
11	$Pd(OAc)_2$	L2	Na_2CO_3	40
12	$Pd(OAc)_2$	L3	Na_2CO_3	35
13	$Pd(PPh_3)_4$	-	K_2CO_3	trace

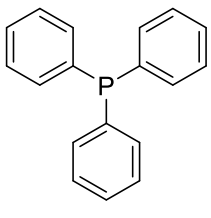
[a]Isolated yield
[b]10 mol % $Pd_2(dba)_3$ as catalyst



L1= 1,10-phenanthrolin



L2= Xantphos



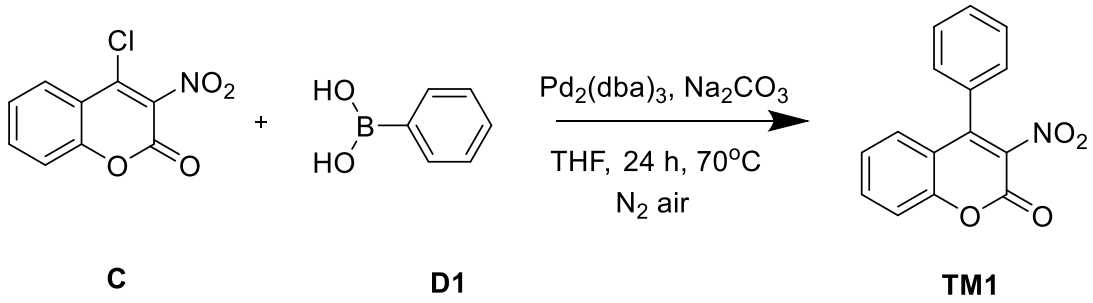
L3= Triphenyl phosphin

Figure 1: Various ligands used in Suzuki coupling

Once these coumarin products were synthesized, a set of experiments were carried out using **C** and **D1** as the model substrate to optimize reaction conditions for the metal-catalyzed coupling reaction, including catalysts, bases, and solvents (scheme-4). $Pd_2(dba)_3$ was the best catalyst among all the three palladium catalysts tested as shown in Table-1. Subsequently, the effect of ligands was further investigated (figure-1); but in $Pd_2(dba)_3$ have not required any type of ligand because of Pd(0). Na_2CO_3 emerged as base of choice for the coupling reaction among the several bases used (Table-1). The effect of solvent was also investigated, and THF was found to be the best solvent at 70°C under N_2 air (Table-2).

Table 2: Screening of solvent for coupling reaction

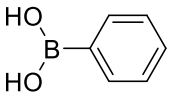
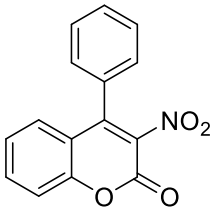
Entry	Solvent	Conversation
1	DMF	82
2	1,4-dioxane	50
3	**THF**	**88**
4	DMF:water	75



C **D1** **TM1**

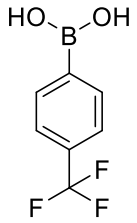
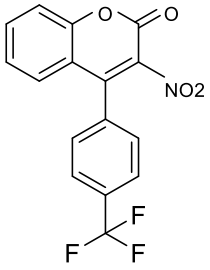
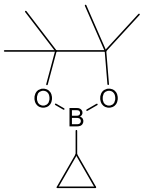
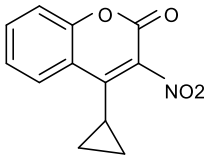
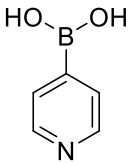
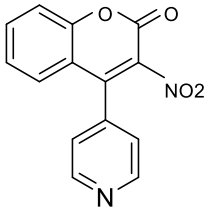
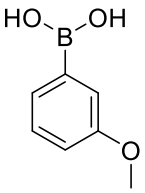
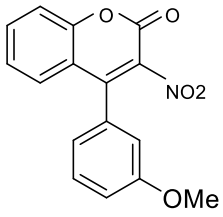
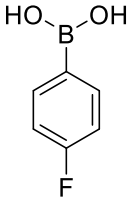
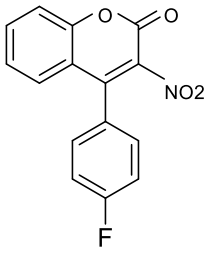
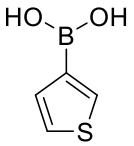
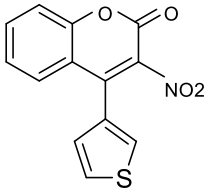
Scheme 4

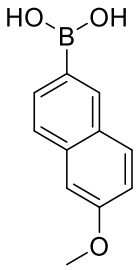
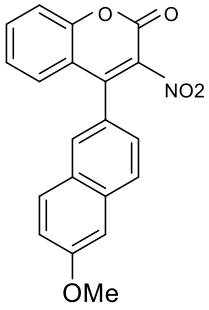
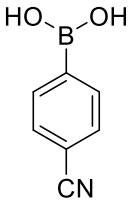
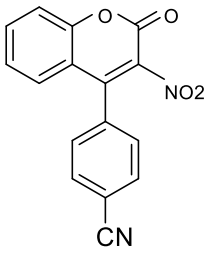
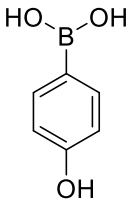
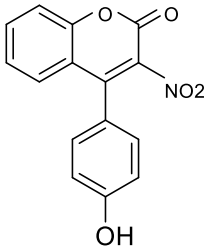
Table 3: Palladium-Catalyzed Direct 4-Arylation/alkylation of 4-chloro 3-nitroCoumarin with Different Boronic acids/esters

Entry	Boronic acid or ester	Product	Yield[a]
1			88

D1

TM1

2	 **D2**	 **TM2**	85
3	 **D3**	 **TM3**	87
4	 **D4**	 **TM4**	83
5	 **D5**	 **TM5**	78
6	 **D6**	 **TM6**	76
7	 **D7**	 **TM7**	74

8	 D8	 TM8	85
9	 D9	 TM9	79
10	 D10	 TM-10	80

[a]Isolated yield

III. Experimental section

All reagents were obtained from sigma-Aldrich and spectrochem India (>99%) and used without further any purification. Analytical thin layer chromatography (TLC) was carried out with silica gel GF 254 precoated plates. Visualization was accomplished with a UV lamp. The reactions were carried out under N_2 atmosphere, and the products were isolated by column chromatography on silica gel (60−120 mesh) using n-haxane and ethyl acetate. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra in DMSO-d_6 as solvent were determined. Chemical shifts are reported in ppm with TMS as reference standard.GC−MS data were also performed.

Synthesis of 4-hydroxy coumarin

Phenol (0.1 mole) and malonic acid (0.1 mole) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 gm, 0.33 mole) which was preheated to get rid of any moisture. The reaction mixture was heated on a water bath at 70^{0}C for 8-10 hours. It was cooled and decomposed with ice and water to afford buff-yellow colored solid. The solid was then filtered and washed thoroughly with water. It was then triturated with 10% sodium carbonate solution and filtered. The filtrate was slowly acidified with dilute HCl till the effervescence ceased. The product was filtered, dried and recrystallized with methanol.

Synthesis of 4-hydroxy 3-nitro coumarin

4-hydroxy3-nitrocoumarins were prepared by heating the corresponding 4-hydroxycoumarins in with HNO_3 and acetic acid at 80-85°C for 1.5 hour. Mixture of 2 equivalent nitric acid and acetic acid was mixed with 4-hydroxy coumarin and acetic acid at 80-85^{0}C temperature. The reaction mass was heated at 80-85^{0}C for 1.5 hours. After completion of the reaction, reaction mass was cooled at room temperature and poured into crushed ice than filtered and washed with water to afford yellow colored solids of 4-hydroxy 3-nitro coumarins.

Synthesis of 4-chloro 3-nitro coumarin

Mixture of DMF and $POCl_3$ (2.5 equivalent) cooled at 0 °C for 20 min then it was stirred at room temperature for 15 min followed by dropwise addition of 4-hydroxy 3-nitrocoumarin dissolved in minimum quantity of DMF. Reaction mixture stirred at R.T. for 2 hour. After completion of reaction, it was poured into the ice and filtered. Solid mass is washed with water to afford yellowish 4-chloro 3-nitrocoumarin.

General Procedure for Palladium-Catalyzed Preparation of 4-aryl/alkyl coumarins

A dried Schlenk test tube containing a magnetic stirring bar was charged under N_2 air with coumarins (0.3 mmol), aryl/alkyl boronic acids (0.9 mmol), $Pd_2(dba)_3$ (10 mol %), and dry THF (2.0 mL). Then, the N_2 was introduced to the tube to form an N_2 balloon. The tube was sealed, and the mixture was treated at 70 °C for 24 h. The resulting mixture was allowed to room temperature and extracted with ethyl acetate three times. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with n-haxane/EtOAc (7:3) to afford the desired product.

Spectral data of the synthesized compounds [TM-01 to 10].

4-cyclopropyl-3-nitro-2H-chromen-2-one.[TM-3]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give a pale yellow solid, 87% yield. mp 50-51°C; R_f 0.22 (9:1 DCM-MeOH); IR (KBr) ν: 3200(aliphatic CH stretching), 3186 (aromatic CH stretching),3149, 3078, 3012,2845,1735, 1752(ester C=O stretching),1579,1668,1467 (aromatic carbon skeleton, C=C stretching) ,1310, 1249, 1014, 819(aromatic CH bending, out of plane), 777, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−8.02 (m, 1H), 7.80−7.85 (m, 1H), 7.36-7.49 (m, 2H), 1.22-1.34 (m, 1H), 0.85-0.89 (d, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.28, 160.06, 146.16, 132.09, 131.77, 130.66, 129.73, 125.49, 116.81, 113.84, 18.13; MS (EI) m/z = 231[M^+].

4-(3-methoxyphenyl)-3-nitro-2H-chromen-2-one.[TM-5]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 3-methoxy-phenylboronic acid to give a pale yellow solid, 78% yield. mp 85-87°C; R_f 0.25 (9:1 DCM-MeOH); IR (KBr) ν: 3186(aromatic CH stretching), 3149, 3078, 3012,1735, 1752(ester C=O stretching),1579,1668,1467(aromatic carbon skeleton, C=C stretching),1310, 1249, 1014, 819(aromatic CH bending, out of plane), 777, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.81 (m, 2H), 7.40−7.48 (m, 2H), 7.38 (m, 1H), 6.93-6.98 (m, 3H), 3.80-3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.86, 155.06, 152.96, 151.09, 139.67, 130.66, 125.73, 121.91, 121.65, 120.89, 120.02, 114.87, 113.69, 110.24, 109.20, 63.15; MS (EI) m/z = 297[M^+].

4-(4-hydroxyphenyl)-3-nitro-2H-chromen-2-one.[TM-10]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 4-hydroxy-phenylboronic acid to give a pale yellow solid. 80% yield: mp 58-60°C; R_f 0.30 (9:1 DCM-MeOH); IR (KBr) ν: 3312(Ar-oh),3250,3186, 3149(aromatic CH stretching), 3078, 3012,1735, 1752(ester C=O stretching),1579, 1668,1467(aromatic carbon skeleton, C=C stretching),1310, 1249, 1014, 819(aromatic CH bending, out of plane), 777, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.84 (s, 1H), 7.90 (m, 4H), 7.40-7.49 (m, 2H), 6.98-7.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.07, 162.00, 160.47, 158.05, 131.03, 130.62, 129.73, 126.13, 125.55, 125.35, 124.56, 122.22, 120.81, 118.56, 110.56; MS (EI) m/z = 283[M^+].

3-nitro-4-phenyl-2H-chromen-2-one.[TM-1]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with phenylboronic acid to give a pale yellow solid, 88% yield: mp 92-93°C; R_f0.24 (9:1 DCM-MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 1H, j = 8 Hz), 7.70-7.74 (m, 1H, j = 8 Hz), 7.30-7.39 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.16, 141.06, 133.96, 132.09, 131.77, 130.66, 129.73, 125.49, 125.45, 125.17, 123.99, 122.46,119.26,116.81,113.84; IR (KBr) ν: 3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}; MS (EI) m/z = 267[M^+].

3-nitro-4-(4-(trifluoromethyl)phenyl)-2H-chromen-2-one.[TM-2]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 4-trifloro-phenylboronic acid to give a pale yellow solid, 85% yield: mp 85-86°C; R_f 0.25 (9:1 DCM-MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 1H, j = 8 Hz), 7.70-7.74 (m, 1H, j = 8 Hz), 7.39-7.42 (m, 4H), 7.25-7.27 (dd, 2H, j=8Hz) ; IR (KBr) ν: 3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}; MS (EI) m/z = 335[M$^+$].

3-nitro-4-(pyridin-4-yl)-2H-chromen-2-one.[TM-4]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with pyridine-4-ylboronic acid to give a pale yellow solid, 83% yield: mp 69-70°C; R_f 0.25 (9:1 DCM-MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.60 (dd, 2H, j=8 Hz), 7.80-7.84 (m, 1H, j = 8 Hz), 7.70-7.74 (m, 1H, j = 8 Hz), 7.39-7.42 (m, 4H) ; IR (KBr) ν: 3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}; MS (EI) m/z = 268[M$^+$].

4-(4-fluorophenyl)-3-nitro-2H-chromen-2-one.[TM-6]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 4-floro-phenylboronic acid to give a pale yellow solid, 76% yield: mp 82-83°C; R_f 0.25 (9:1 DCM-MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 1H, j = 8 Hz), 7.70-7.74 (m, 1H, j = 8 Hz), 7.24-7.42 (m, 6H) ; IR (KBr) ν: 3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}; MS (EI) m/z = 285[M$^+$].

***3-nitro-4-(thiophen-3-yl)-2H-chromen-2-one*.[TM-7]**

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with thiophen-3-ylboronic acid to give a pale yellow solid, 74% yield: mp 72-73°C; R_f 0.22 (9:1 DCM-MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 1H), 7.68-7.70 (m, 3H), 7.39-7.40 (m, 2H), 7.22-7.23 (dd, 1H, j=8Hz) ; IR (KBr) ν: 3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}; MS (EI) m/z = 273[M$^+$].

4-(6-methoxynaphthalen-2-yl)-3-nitro-2H-chromen-2-one.[TM-8]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with (6-methoxynaphthalen-2-yl)boronic acid to give a pale yellow solid, 85% yield: mp 78-79°C; R_f 0.24 (9:1 DCM-MeOH); IR (KBr) ν3186, 3149, 3078, 3012,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}.

4-(3-nitro-2-oxo-2H-chromen-4-yl)benzonitrile.[TM-9]

The title compound was prepared according to the general procedure for 4-arylated coumarin of coumarin with 4-cyano-phenylboronic acid to give a pale yellow solid, 79% yield: mp 56-58°C; R_f 0.29 (9:1 DCM-MeOH); IR (KBr) ν: 3186, 3149, 3078, 3012,2200,1735, 1752,1579,1668,1467,1310, 1249, 1014, 819, 777, 742 cm^{-1}.

IV. CONCLUSION

In conclusion, we have developed an efficient protocol for the synthesis of 4-aryl/alkyl coumarins via palladium-catalyzed oxidative Suzuki-Miyaura coupling reaction of coumarins and diversely substituted boronic acids (Table-3). The reaction represents a convenient, atom-economic approach with good functional group tolerance. $Pd(PPh_3)_4$ is not suitable catalyst for this reaction because of 4-chloro 3-nitrocoumarin have oxidizing nature itself and $Pd(PPh_3)_4$ oxidized into tri-phenyl phosphine oxide under nitrogen air also.

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