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Palladium catalyzed Suzuki Miyaura cross coupling of 3-chloroisochromen-1-one: synthesis of glomellin and reticulol analogues

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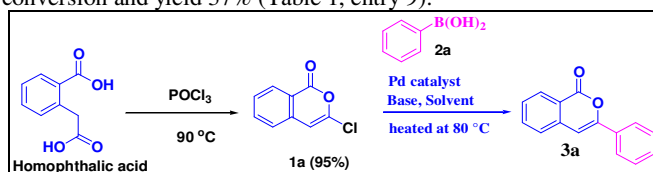
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Abstract A facile protocol has been developed for a series of 3-substituted isochromen-1-ones utilizing Suzuki coupling strategy. The reaction of 3-chloroisochromen-1-one, **1** with different boronic acids utilizing PdCl₂(PPh₃)₂-Ruphos catalytic system gave diversified 3-substituted isochromen-1-ones in excellent yields. The methodology has been utilized in the synthesis of glomellin and reticulol analogues.

There are few illustrations of terminal and internal alkynes as reagents in palladium catalyzed Sonagashira coupling and C-C bond forming reaction where the alkyne functionality is lost in the formation of 3- or 3,4- disubstituted isochromen-1-one ring moiety^{1, 2}. The Suzuki cross coupling methodology is extremely versatile for the generation of C-C bonds.³ Nevertheless; no reports on Suzuki coupling are available in the formation of highly functionalized 3-substituted isochromen-1-ones. Our continuing efforts and interests in metal-catalyzed C-C bond formations⁴⁻¹⁰ and cyclization reactions incited us to investigate the reaction of aryl/heteroaryl/ alkyboronic acids and 3-chloroisochromen-1-one as important motifs for rapid access to known and obscure highly functionalized 3-arylisochromen-1-ones. The application of this strategy in the synthesis of natural isochromen-1-one analogues is examined as well. Notwithstanding this, few exertions have been regulated to investigate a productive catalytic combination in the synthesis of diversified 3-substituted isochromen-1-one.

Results and Discussion

The 3-chloroisochromen-1-one, **1a** and phenylboronic acid, **2a** was picked as a model substrate for the palladium-catalyzed Suzuki coupling reaction, (Scheme 1, Table 1). At first, the reaction was done in the presence of 5 mol% of Pd(OAc)₂, DMF or water as solvent, K₂CO₃ or Na₂CO₃ as a base, but the reaction did not proceed well (Table 1, entries 1-4). The conversion and yield was very less in the absence of ligands. The assessment of the solvents revealed that the transformation was highly sensitive to the reaction medium. The protic polar solvents, for instance, MeOH, EtOH, Dioxane, THF displayed lower reactivity (Table 1, entries 5-8). Gratifyingly, the mixed solvent combination of DMF/H₂O (1:1) gave the best result in conversion and yield 37% (Table 1, entry 9).



Scheme 1. Design of synthesis of 3-substituted isochromen-1-one by a Suzuki coupling reaction

Control experiments revealed that the reaction did not proceed without palladium (Table 1, entry 10). In cross-coupling reactions of organoboron compounds, the presence of a base is essential; as no reaction occurs without a base. Further, many organic compounds are sensitive to bases. Consequently, a careful use of bases is required in such cases, for instance, K₂CO₃, Na₂CO₃, K₃PO₄, Cs₂CO₃, KOBu, Et₃N. The results showed that K₂CO₃ was the best base for the present study with a moderate conversion and 37% yield (Table 1, entry 9). In K₃PO₄ gave 45% yield, likewise in other bases, though conversion is 100 % gave poor yields (Table 1, entries 11-15).

These preliminary reaction conditions inspired us to develop a suitable catalytic combination utilizing ligand mediated Suzuki coupling methods. Interestingly, the exploration of phosphine, bisphosphine ligands (Table 1, entry 16-19) demonstrated that Ruphos was the best ligand with respect to the yield and conversion time utilizing 5mol% Pd(OAc)₂. In the optimization of the reaction condition, we were satisfied to find that the yield was greatly enhanced to 82% (Table 1, entry 19) when DMF-water mixture was utilized as the solvent in just 30min., Sphos, Xphos are comparable, whereas PPh₃, despite a complete conversion gave a lower isolated yield 76% (Table 1, entry 16). The utilization of 10 mol% of Ruphos ligand and K₂CO₃ as the base in DMF solvent condition demonstrated a decent conversion rate in 1h but the isolated yield was moderate 56% (Table 1, entry 20). With this optimized condition in hand, we have tested variations in the amount of palladium loading, reaction time. Increasing the reaction time, Pd loading did not show any increment in the yield and it was moderate in all cases (Table 1, entries 21,22). In the literature, it is reported that utilizing aryl chlorides as a part of Suzuki couplings obliged a strong electron withdrawing substituent on the aryl chloride. Nevertheless, in the present methodology, no such special substitute for the reactivity is involved.

Table 1. Palladium acetate catalyzed Suzuki coupling of 3-chloro-1H-isochromen-1-one with phenyl boronic acid: Optimization of the reaction conditions^a

Entry	Catalyst Pd(OAc) ₂ mol %	Ligand/ mol %	Solvent	Conversion %	Time h	Yield (%)
1	5	-	DMF ^a	Traces	2	-
2	5	-	DMF ^b	Traces	2	-
3	5	-	H ₂ O ^c	20	2	15
4	5	-	H ₂ O ^b	30	2	26
5	5	-	MeOH	10	2	-
6	5	-	EtOH	15	2	-
7	5	-	Dioxane	25	2	18
8	5	-	THF	20	2	16
9	5	No	DMF/H ₂ O	45	2	37
10	0	No	DMF/H ₂ O	NR	2	-
11	5	No	DMF/H ₂ O ^b	100	2	32
12	5	No	DMF/H ₂ O ^c	100	2	45
13	5	No	DMF/H ₂ O ^d	100	2	32
14	5	No	DMF/H ₂ O ^e	100	2	21
15	5	No	DMF/H ₂ O ^f	50	2	35
16	5	PPh ₃ /10	DMF/H ₂ O	100	0.5	76
17	5	X-phos/10	DMF/H ₂ O	100	0.5	81
18	5	S-phos/10	DMF/H ₂ O	100	0.5	79
19	5	Ruphos/10	DMF/ H ₂ O	100	0.5	82
20	5	Ruphos/10	DMF/	80	1	56
21	10	Ruphos/10	DMF/H ₂ O	100	0.5	71
22	5	Ruphos/10	DMF/H ₂ O	100	1	75

The reactions were performed in a round bottomed flask with 3-chloro-1H-isochromen-1-one, **1a** (1 mmol), phenylboronic acid, **2a** (1 mmol), catalyst, ligand, base K₂CO₃ unless otherwise stated and solvent heated for 0.5-2 h. ^aNa₂CO₃, ^bK₂CO₃, ^cK₃PO₄, ^dCS₂CO₃, ^eKOBu, ^fEt₃N

Table 2. PdCl₂(PPh₃)₂ catalyzed Suzuki coupling of 3-chloro-1H-isochromen-1-one, **1a with phenylboronic acid, **2a**: Optimization of the reaction conditions^a**

Entry	Catalyst/ mol %	Ligand/ mol %	Solvent	Conversion n %	time	Yield (%)
1	PdCl ₂ (PPh ₃) ₂ /10	No	DMF	25	2 h	18
2	PdCl ₂ (PPh ₃) ₂ /10	No	DMF ^b	40	2 h	34
3	PdCl ₂ (PPh ₃) ₂ /10	No	DMF/H ₂ O	60	2 h	56
4	PdCl ₂ (PPh ₃) ₂ /10	PPh ₃ /10	DMF/H ₂ O	100	0.5	82
5	PdCl ₂ (PPh ₃) ₂ /5	PPh ₃ /10	DMF/H ₂ O	100	0.5	84
6	PdCl ₂ (PPh ₃) ₂ /5	Ruphos/10	DMF/H ₂ O	100	0.5	95
7	PdCl ₂ (PPh ₃) ₂ /5	Ruphos/5	DMF/H ₂ O	100	0.5	93
8	PdCl ₂ (PPh ₃) ₂ /5	Ruphos/15	DMF/H ₂ O	100	0.5	94

The reactions were performed in a round bottomed flask with 3-chloro-1H-isochromen-1-one, **1a** (1 mmol), phenylboronic acid, **2a** (1 mmol), catalyst, ligand, base (K₂CO₃) unless otherwise stated, and solvent heated for ½ - 2 h ^b Na₂CO₃

Encouraged by these initial perceptions, we focused on the improvisation of the yield by utilizing different palladium sources. Correspondingly, as in palladium acetate, we have tested utilizing bis-triphenylphosphine palladium dichloride catalyst and were pleased to find that, the reaction behaves in a comparative way when utilizing 10 mol% of PdCl₂(PPh₃)₂, either K₂CO₃ or Na₂CO₃ as the base and DMF with or without aqueous conditions heated at 80°C (Table 2, entries 1-3). Nonetheless, the reaction worked well in the presence of phosphine ligand and the yield was also good comparable to palladium acetate source. Further, there was no impact on the variation of the amount of palladium load (Table 2, entries 4, 5). To enhance the yield, we have done reactions utilizing 10 or 5 mol% of Ruphos ligand, 5 mol% of PdCl₂(PPh₃)₂ catalysts, K₂CO₃ as the base and DMF: water mixture as a solvent which produced an excellent yield (93-95%) and was also consistent (Table 2, entry 6-8).

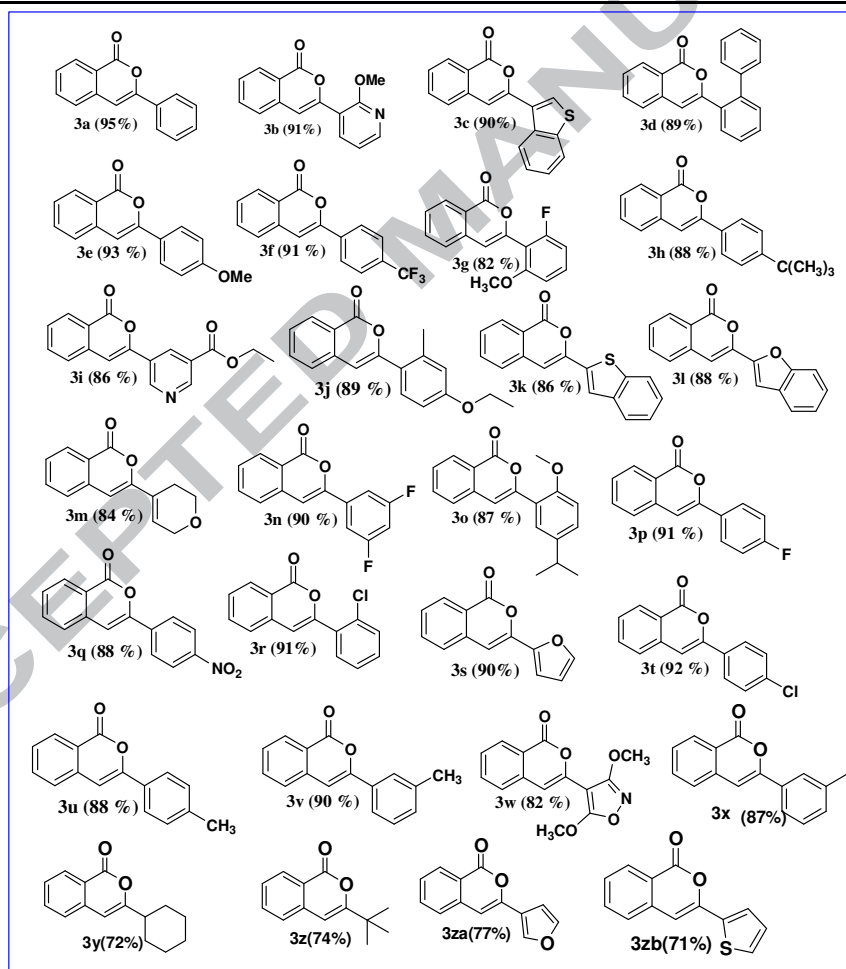
In continuation, with this excellent result in hand, we have further extended the optimization study utilizing Palladium tetrakis. Nonetheless, in the Pd(PPh₃)₄, the conversion was complete and the desired product was obtained with a good yield. We noticed that the Suzuki coupling of 3-chloro-1H-isochromen-1-one, **1a** with phenyl boronic acid, **2a** using 10 mol % of Palladium tetrakis catalyst, K₂CO₃ as the base and DMF: water mixture as a solvent afforded a 75% yield (Table 3, entry 3). Further, when reduced the amount of palladium load to 5 mol%, observed a 67% yield (Table 3, entry 4). Based on our earlier observations, this reaction required additional ligand to drive the reaction for better conversion and invariably for getting an excellent yield and purity. An extended the optimization study using Palladium tetrakis and Ruphos ligand with variations in the amount of load was carried out. We are pleased to inform that, the result was an excellent as that of Palladium dikis (Table 3, entries 7-10). The complete screening results are summarized in Table 3.

Table 3. Pd(PPh₃)₄ catalyzed Suzuki coupling of 3-chloro-1*H*-isochromen-1-one, **1a** with phenylboronic acid, **2a**: Optimization of the reaction conditions^a

Entry	Catalyst/ mol %	Ligand/ mol %	Solvent	Conv %	Time h,	Yield (%)
1	Pd(PPh ₃) ₄ /10	No	H ₂ O	50	1	45
2	Pd(PPh ₃) ₄ /10	No	DMF	65	1	57
3	Pd(PPh ₃) ₄ /10	No	DMF/H ₂ O	100	1	75
4	Pd(PPh ₃) ₄ /5	No	DMF/H ₂ O	85	1	67
5	Pd(PPh ₃) ₄ /10	PPh ₃ /10	DMF/H ₂ O	100	0.5	76
6	Pd(PPh ₃) ₄ /5	PPh ₃ /10	DMF/H ₂ O	100	0.5	80
7	Pd(PPh ₃) ₄ /10	Ruphos/10	DMF/H ₂ O	100	0.5	86
8	Pd(PPh ₃) ₄ /5	Ruphos/10	DMF/H ₂ O	100	0.5	92
9	Pd(PPh ₃) ₄ /5	Ruphos/5	DMF/H ₂ O	100	0.5	92
10	Pd(PPh ₃) ₄ /5	Ruphos/15	DMF/H ₂ O	100	0.5	91

^aThe reactions were performed in a round bottomed flask with 3-chloro-1*H*-isochromen-1-one, **1a** (1 mmol), phenylboronic acid, **2a** (1 mmol), catalyst, ligand, base and solvent heated for ½ h-2h

Table 4 Synthesis of 3-Substituted isocoumarins from 3-chloro-1*H*-isochromen-1-one^a



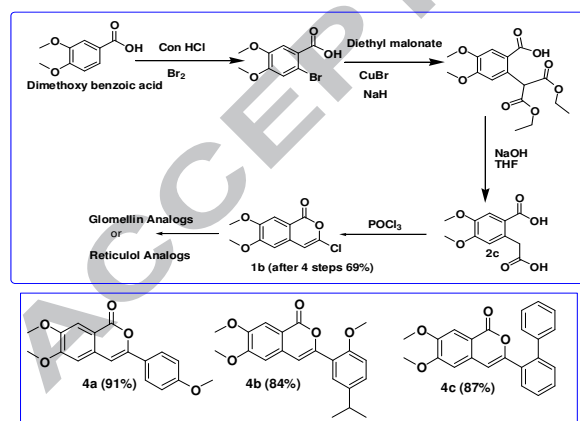
^aThe reactions were performed in a round bottomed flask with 3-chloro-1*H*-isochromen-1-one, **1a** (1 mmol), aliphatic/aryl/hetero/alicyclic boronic acid, **2** (1 mmol), PdCl₂(PPh₃)₂ catalyst (5 mol %), Ruphos ligand (5 mol %), K₂CO₃ (2.0 eq.) base and DMF: water mixture (9:1, 15 v) solvent, heated at 80 °C for 30 min.

The optimization studies envisaged that the use of PdCl₂(PPh₃)₂-Ruphos catalytic system, K₂CO₃ as the base and DMF-water mixture conditions offered a greater efficiency in the synthesis of diversified 3-substituted isochromen-1-one with amazing yields. The

transformation proceeded with an excellent conversion and yield regardless of the electronic properties of the substituent (Table 4). With this optimized condition in hand, the Suzuki coupling of 3-chloro-1*H*-isochromen-1-one was done with various boronic acids using 5 mol% of PdCl₂(PPh₃)₂ catalyst, 5 mol% of Ruphos ligand, 2.0 eq. of base and DMF : water mixture (10:1 ratio) with heating at 80 °C for 30 min. We are pleased to inform that the Suzuki coupling reaction worked efficiently well in all the cases and the yield was consistent and excellent. This novel and efficient method was employed with various substituted phenylboronic acids **2a-z** with 3-chloroisochromen-1-one (**1a**) under the optimized reaction conditions. Gratifyingly, excellent yields were observed for these substrates with electron-donating or electron-withdrawing groups and the results are summarized in Table 4. Current protocol is highly efficient, economical, environmentally benign and practical for the arylboronic acids with electron-donating or electron-withdrawing groups as well with other *ortho*-substitutions. The transformation proceeded with an excellent conversion and yield regardless of the electronic properties of the substituent.

Encouraged by the resulting outcomes, we were interested in extending the scope of the reaction towards accomplishing the natural isochromen-1-one analogues. Finally, we have demonstrated the utility of the current benign protocol in the synthesis of natural isochromen-1-ones, namely glomellin and reticulol analogues as depicted in scheme 2. The dimethoxyhomophthalic acid required for the natural isochromen-1-one was obtained as reported elsewhere.^{11, 12}

Initially, the bromination of the dimethoxybenzoic acid using Conc.HCl and bromine resulted in a 2-bromodimethoxybenzoic acid, which, when reacted with diethylmalonate in the presence of Cu(I)/base combination offered a corresponding intermediate that in turn hydrolyzed to the homophthalic acid analogue. The as obtained dimethoxyhomophthalic acid when reacted with POCl₃ resulted in the active starting material chloro derivatives, **1b** for the functionalized isochromen-ones, namely the glomellin and reticulol analogues as depicted in scheme 2. Accordingly, Thungberginol A, B, Cytogenin, etc. may also be obtained following the above protocol¹², which are under progress in our laboratory.



Scheme 2. Design of natural 3-substituted isochromen-1-one- Glomellin and Reticulol analogues by a Suzuki coupling reaction

Further, we were interested in a sustainable and environmentally friendly approach for the synthesis of the desired target materials. With this intention in mind, the intermolecular competition experiments were carried out initially using mono equivalents of each chloro derivatives **1a** and **1b** and biequivalent of

boronic acid **2e** and the desired products **3e** and **4a**, yields were determined by isolating yield.

The results are presented in supporting documents. Interestingly, the desired products are obtained with one-pot as excellent yields with the above optimised reaction conditions in both the intermolecular experiments which suggests that the intermolecular reactions approach may effectively be used in the preparation of several isochromen-1-ones simultaneously without any practical difficulty through one-pot multi-product formation, reduced catalyst loading, lesser reaction time period, and a reduction in the number of column purifications and so on. The proposed mechanism of the reaction is depicted in scheme 5 (see SI) .

Conclusions

To conclude, we have successfully developed a novel and efficient, experimentally simple, high yielding, PdCl₂(PPh₃)₂-Ruphos catalyzed Suzuki coupling of 3-chloroisochromen-1-one with aryl boronic acids under mild conditions in the synthesis of diversified 3-disubstituted isocoumarins, in the presence K₂CO₃ base and DMF: water mixture. The catalytic reaction proceeds smoothly and provides various 3-substituted isochromen-1-ones through C-C bond formation with good yields. The highlights of this catalytic combination are high catalytic activity, ready availability of the catalyst and aqueous mediated reaction conditions. The methodology is entirely new for the synthesis of diversified 3-disubstituted isocoumarins. More applications of this methodology, in natural product synthesis, are in progress.

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12. Experimental Section-Procedure for the synthesis of 3-chloro isochromen-1-one, **1a**

-See supporting document .

Preparation of 4,5-dimethoxyhomophthalic acid, 3-chloro isochromen-1-one, **1b** and intermolecular competition experiments:

-See supporting document.

Typical procedure for the palladium-catalyzed synthesis of 3-phenyl isochromen-1-one, **3a**

A sealed tube containing PdCl₂(PPh₃)₂ (38.96 mg, 0.055 mmol, 5 mol %), Ruphos (5 mol%) 3-Chloroisochromen-1-one **1a** (200.45mg, 1.11 mmol), arylboronic acid **2a** (1.22 mmol) and K₂CO₃ (306.82 mg, 2.22 mmol) were purged with nitrogen gas three times. Then, DMF (3.00 mL) was added with a syringe. The reaction mixture was stirred at 80 °C for 30 min and was diluted with ethyl acetate (30 mL). The mixture was filtered through a celite bed and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified on a silica gel column using hexane/ethyl acetate as eluent to afford the desired product, **3a**.

-See supporting document for spectral data of compounds **3a-zb** and **4a-c**.

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#Equally contributed

