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Efficient copper-free $Pd(OAc)_2$/Ruphos-catalyzed Sonogashira coupling in the preparation of 3′-hydroxycorfin and gymnopalynes A analogues

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ABSTRACT

An efficient method involving copper-free $Pd(OAc)_2$/Ruphos-catalyzed Sonogashira coupling strategy for a variety of 3-alkynyl isochromen-1-ones has been developed. Sonogashira coupling in the presence of catalytic system—$Pd(OAc)_2$/Ruphos, Et_3N base, and tetrahydrofuran solvent under aqueous and room temperature conditions, provided novel 3-(alkynyl)-1H-isochromen-1-ones in excellent yields. The methodology has also been extended toward natural isochromen-1-one–3′-hydroxycorfin and gymnopalynes A analogues.

Introduction

The prevalence of isochromen-1-one moiety in numerous natural products which exhibit a wide range of biological activities has generated a continued and enormous interest among synthetic and medicinal chemists.[1] Among the various substituted isochromen-1-ones, the 3-substituted isochromen-1-ones are important building blocks in many biologically active natural products.[2] The 3-substituted isochromen-1-ones showed anti HIV activity in vitro, diuretic, antihypertensive, β-sympatholytic, anticorrosive, laxatives, asthmolytic, phytotoxic, and were found to be useful in the treatment of emphysema.[3] Likewise, they exhibit a broad range of pharmacological activities including antimalarial,[4] antimicrobial,[5] immunomodulatory,[6] antifungal,[7] anti-inflammatory,[8] phytotoxic,[9] antiangiogenic,[10] cytotoxic, and mutagenic activities.[11] Isochromen-1-ones act as a lead compound for the identification of insecticides which selectively bind at the insect GABA receptor.[12]

A few naturally occurring 3-butylisocoumrins, corfins were isolated from lipophilic extracts of aerial as well as underground organs and 3'-hydroxycorfins from the roots of *Chamaemelum mixtum*.[13] In our continued research interests,[14] in order to explore the scope of the Sonogashira coupling, the naturally occurring acetylenic compounds hydroxyl corfin analogues were attempted as summarized in Scheme 1.

With regard to the hydroxyl corfin derivatives optimization of the reaction conditions was done (Table 1), initially the reactions were performed using 3-chloroisocoumarin, **1a**, propargyl alcohol, **2f,** $Pd(OAc)_2$/Ruphos catalytic, and reflux conditions. Unfortunately, the trials have failed to offer the desired product quantitatively, although the conversion rate was 100% (Table 1, entries 1–6) attributable to high temperature, for example, at 80 °C, the alkynyl alcohols are highly reactive to offer the undesired product such as the self coupling products in major yields. Similar observations were noticed while using Oxydiphos (or DPEPhos), Xphos, and Sphos ligands (Table 1, entries 1–5). To achieve the Sonogashira coupling of alcoholic acetylenic compounds with 3-chloro-1*H*-isochromen-1-one efficiently, the influence of temperature from 0 to 70 °C has been explored as in Table 1 (entries 5–14). To our surprise, the desired propargyl alcohol **3f** was achieved at a reduced temperature. The results revealed that the optimal temperature for the coupling reaction was found to be 20–30 °C. Below this temperature the substrates did not react effectively to offer the quantitative yield, and above this temperature a decomposition of alkynyl

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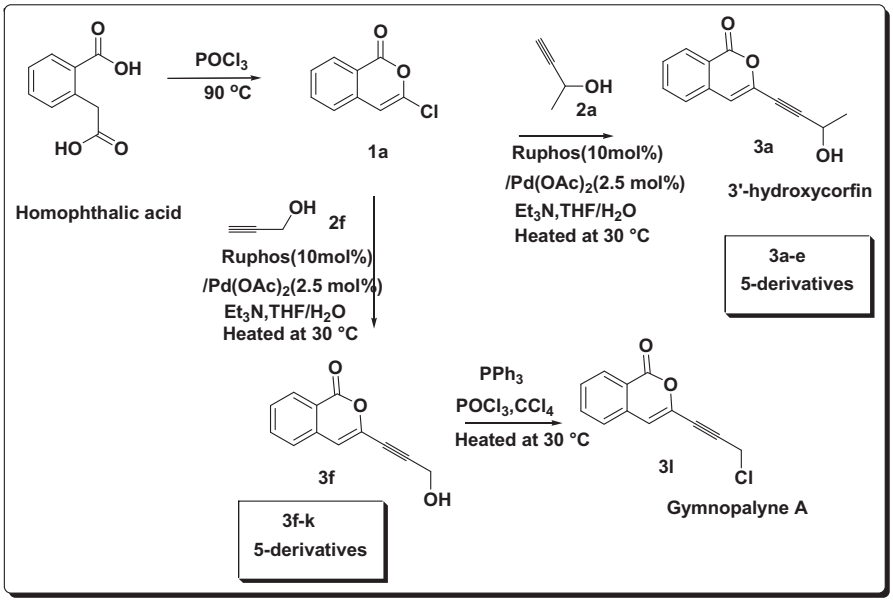
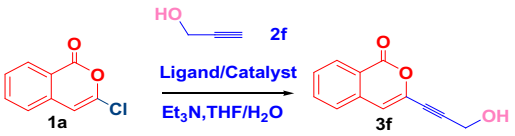


Scheme 1. Synthesis of 3′-hydroxycorfin and gymnopalynes A analogues[a].

Table 1
Sonogashira coupling of 3-chloro-1*H*-isochromen-1-one with propargyl alcohol: Optimization of the reaction conditions[a]



Entry	Catalyst	Ligand	Temp (°C)	Time (h)	Isolated yield (%)
1	$Pd(OAc)_2$	Ruphos	80	1	Trace[b]
2	$Pd(OAc)_2$	Oxydiphos	80	1	Trace[b]
3	$Pd(OAc)_2$	Xphos	80	1	Trace[b]
4	$Pd(OAc)_2$	Sphos	80	1	Trace[b]
5	$Pd(OAc)_2$	Ruphos	70	1	Trace[b]
6	$Pd(OAc)_2$	Ruphos	60	1	Trace[b]
7	$Pd(OAc)_2$	Ruphos	50	7	55
8	$Pd(OAc)_2$	Ruphos	40	7	65
9	$Pd(OAc)_2$	Ruphos	35	7	76
10	$Pd(OAc)_2$	Ruphos	30	7	92
11	$Pd(OAc)_2$	Ruphos	25	12	79
12	$Pd(OAc)_2$	Ruphos	20	12	65
13	$Pd(OAc)_2$	Ruphos	10	12	40
14	$Pd(OAc)_2$	Ruphos	0	12	Trace
15	$Pd(OAc)_2$	Oxydiphos	25	7	60
16	$Pd(OAc)_2$	Xphos	25	7	64
17	$Pd(OAc)_2$	Sphos	25	7	61

[a] Reaction conditions: **1a** (1.11 mmol), **2f** (1.22 mmol), base Et_3N, $Pd(OAc)_2$ (2.5 mol %), ligand (10 mol %), THF (5 mL), degassed water (0.5 mL).
[b] At 80 °C, the alkynyl alcohols undergo self coupling, with traces of inseparable desired product.

substrates and products was observed. With this optimized condition in hand the role of ligands such as, Oxydiphos, Xphos, and Sphos were then explored. Moderate yields were obtained and the best emerged out of the ligands as Ruphos (Table 1, entries 15–17). The hydroxyl corfin derivatives **3a–e** were successfully attained following the optimized reaction condition as tabulated in Tables 1 and 2).

Encouraged by the results, further successful attempts were made to achieve the recently isolated Gymnopalyne A,[15] a chloropropynyl-isocoumarin antibiotics from cultures of the basidiomycete *Gymnopus* sp. as depicted in Scheme 1. The derivatives of Gymnopalyne A, for example, the acetylenic compounds **3g–k** were successfully achieved as tabulated in Table 3. The Gymnopalyne A, **3l** was also achieved as depicted in Scheme 1 from the corresponding hydroxyl derivative using triphenylphosphine, $POCl_3$, and halide solvent.[16,17] All the synthesized target compounds were characterized by NMR spectroscopy.

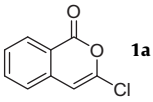
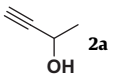
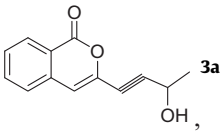
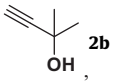
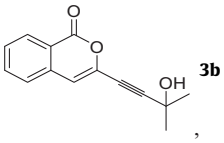
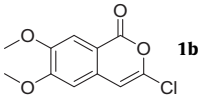
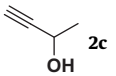
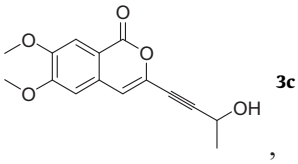
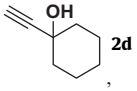
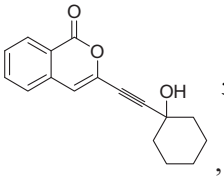
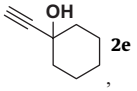
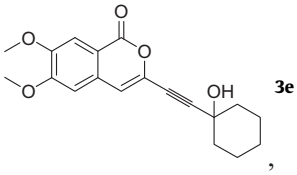
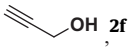
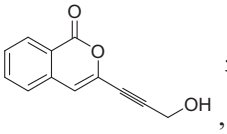
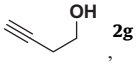
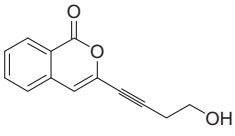
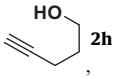
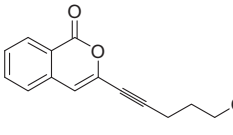
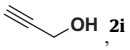
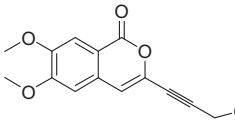
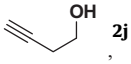
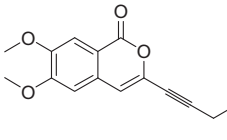
The proposed mechanism of the reaction is delineated in Scheme 2. The catalytically active Pd^0 species **I**, is stabilized by the ligand present. The Sonogashira coupling catalytic cycle was initiated by the oxidative addition of aryl halides to species **I**, forming the adduct **II** as a homogeneous Pd^{II} species followed by a reversible coordination of the alkyne to **II** producing an alkyne–Pd^{II} complex **III**. The base then abstracts a proton from coordinated alkyne, forming the palladium–acetylide complex **IV**, from which the cross-coupled product **V** is obtained by reductive elimination and regenerating the catalyst species **I**.

Table 2
Effect of solvent

Entry	Catalyst	Ligand	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	$Pd(OAc)_2$	Ruphos	Acetonitrile	30	7	87
2	$Pd(OAc)_2$	Ruphos	1,4-Dioxane	30	7	84
3	$Pd(OAc)_2$	Ruphos	1,4-Dioxane	80	1	Trace
4	$Pd(OAc)_2$	Ruphos	DMF	30	7	78
5	$Pd(OAc)_2$	Ruphos	DMF	80	1	Trace
6	$Pd(OAc)_2$	Ruphos	TEA	30	7	85
7	$Pd(OAc)_2$	Ruphos	THF	30	7	92
8	$Pd(OAc)_2$	Ruphos	THF	70	1	Trace

Reaction conditions: **1a** (1.11 mmol), **2f** (1.22 mmol), base Et_3N, $Pd(OAc)_2$ (2.5 mol %), Ruphos (10 mol %), degassed water (0.5 mL).

Table 3
Sonogashira coupling of 3-chloro-1*H*-isochromen-1-one with alkynes

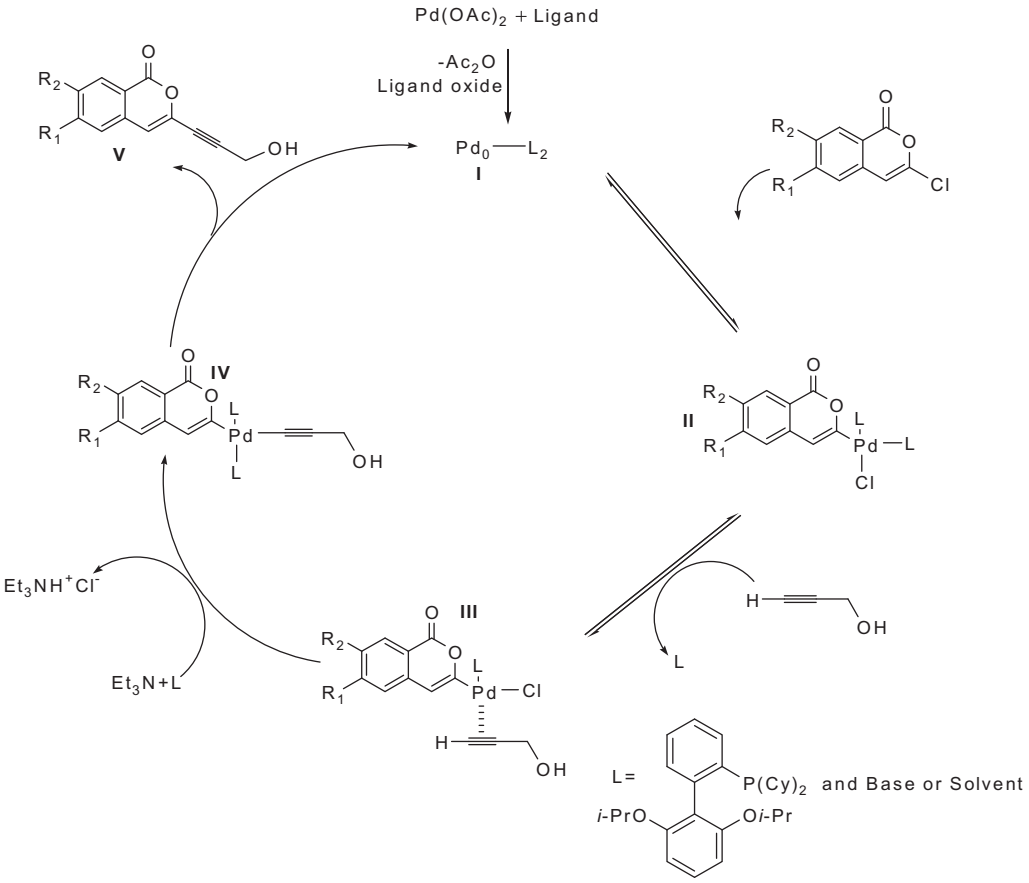
Entry	Chloroisocoumarin	Alkynes	Product	Yield (%)
3′-Hydroxycorfin analogs				
1	 **1a**	 **2a** ,	 **3a** ,	89
2	**1a**	 **2b** ,	 **3b** ,	86
3	 **1b**	 **2c** ,	 **3c** ,	85
4	**1a**	 **2d** ,	 **3d** ,	83
5	**1b**	 **2e** ,	 **3e** ,	80
Gymnopalyne A analogs				
6	**1a**	 **2f** ,	 **3f** ,	92
7	**1a**	 **2g** ,	 **3g** ,	90
8	**1a**	 **2h** ,	 **3h** ,	81
9	**1b**	 **2i** ,	 **3i** ,	90
10	**1b**	 **2j** ,	 **3j** ,	84

(*continued on next page*)

Table 3 (*continued*)

Entry	Chloroisocoumarin	Alkynes	Product	Yield (%)
11	**1b**	HO **2k** ,	**3k** ,	79

Reaction conditions: **1a** or **1b** (1.11 mmol), alkyne **2** (1.22 mmol), base Et_3N, Pd $(OAc)_2$ (2.5 mol %), Ruphos (10 mol %), THF (5 mL), degassed water (0.5 mL), refluxed at room temperature, 7 h.



Scheme 2. Proposed mechanism of the reaction.

Conclusions

The present methodology is highly attractive for the exploitation of differently substituted isocoumarins and it may be utilized for the synthesis of naturally occurring bioactive various 3-substituted isocoumarins similar to our successful attempt of 3′-hydroxycorfin, Gymnopalyne A derivatives and so on.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.059.

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16. Procedure for the synthesis of 3-chloro isochromen-1-one, **1a**. A mixture of homophthalic acid and phosphorus oxychloride was taken in an RB flask. The reaction mixture was stirred at 80 °C for 3 h and monitored frequently for the completion of the reaction and then was quenched with crushed ice. The contents were left aside for complete precipitation of the crude desired products. The mixture was then filtered through a Buchner funnel and the residue, after drying, was purified on a silica gel column using hexane/ethyl acetate as eluent to afford the desired 3-chloroisochromen-1-ones ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.31 (d, J = 7.8 Hz, 1H), 7.91–7.88 (m, 2H), 7.75–7.71 (dt, J = 7.96, 0.56 Hz, 1H), 7.52–7.43 (m, 5H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.6, 136.5, 133.8, 130.9, 128.9, 128.7, 127.8, 127.2, 124.9, 124.2, 119.6, 100.8.
Preparation of **1b** is delineated in the Supporting information, SI.
General procedure for hydroxycorfin derivatives: $Pd(OAc)_2$ (7 mg, 0.031 mmol, 2.5 mol %), 3-chloroisochromen-1-one **1a** (200.45 mg, 1.11 mmol), propargyl alcohol, **2f** (1.22 mmol), Ruphos (52 mg, 0.11 mmol, 10 mol %), and triethyl amine (224.2 mg, 2.21 mmol) were purged in a sealed tube with nitrogen gas three times. Then degased water (0.5 mL), THF (5.00 mL) was added with a syringe. The reaction mixture was stirred at rt for 7 h and was diluted with ethyl acetate (30 mL). The mixture was filtered through 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, **3f** (203 mg, 92% yield) **(3f)** yellow oil, (203 mg, 92% yield) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 7.98 Hz, 1H), 7.73 (dt, J = 7.57, 0.90 Hz, 1H), 7.4 (dt, J = 7.85, 0.81 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 4.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 137.4, 136.3, 135.0, 129.9, 129.4, 125.9, 121.5, 111.8, 91.9, 78.4, 51.3; IR (v, cm^{-1}) 3072, 2960, 2929, 2856, 2426, 2227, 1980, 1726, 1708, 1703, 1681, 1625, 1602, 1481, 1444, 1384, 1338, 1325, 1300, 1267, 1219, 1184, 1068, 1022, 989, 885, 852, 752, 686, 655, 617, 574, 532; UPLC–MS: m/e 201.0, $C_{12}H_8O_3$ required Mol.wt: 200.19.
(**3a**) Yellow solid, (210 mg, 89% yield) mp 77–79 °C**,** $_1$H NMR (400 MHz, CDCl3) δ 8.28–8.27 (d, J = 7.88 Hz, 1H), 7.74–7.70 (t, J = 7.49 Hz, 1H), 7.56–7.52 (t, J = 7.70 Hz, 1H), 7.42–7.40 (d, J = 7.70 Hz, 1H), 6.72 (s, 1H), 4.79–4.74 (q, J = 6.48 Hz, 1H), 1.58–1.56 (d, J = 6.60 Hz, 3H).; ^{13}C NMR (100 MHz, CDCl3) δ 161.6, 137.5, 136.4, 135.0, 129.8, 129.3, 125.8, 121.5, 111.6, 95.4, 58.6, 23.8.; IR (v, cm^{-1}) 3437, 3072, 2983, 2872, 2225, 1998, 1730, 1687, 1627, 1614, 1600, 1562, 1481, 1384, 1336, 1296, 1219, 1178, 1099, 1082, 1051, 1018, 981, 916, 877, 833, 763, 686, 621, 518. UPLC–MS: m/e 215.0, $C_{13}H_{10}O_3$ required Mol. wt:214.22.
(**3b**) Yellow solid, (217 mg, 86% yield) mp 77–80 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.92 Hz, 1H), 7.71 (t, J = 7.61 Hz, 1H), 7.53 (t, J = 7.69 Hz, 1H), 7.40 (d, J = 7.81 Hz, 1H), 6.70 (s, 1H), 1.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 137.7, 136.5, 134.9, 129.8, 129.2, 125.8, 121.4, 111.4, 98.1, 75.1, 65.5, 30.9; UPLC–MS: m/e 229.1; $C_{14}H_{12}O_3$ required Mol. wt: 228.24.
For other derivatives see SI.
17. Preparation of Gymnopalyne A: 20 mL of carbon tetra chloride, triphenyl phosphine (100 mg, 0.381 mmol), and $POCl_3$ (2 g,0.013 mmol) were added to the propargyl alcohol derivative **3f**, (250 mg) and stirred at room temperature for 1 h. The completion of the reaction was monitored by TLC then reaction mixture was quenched with ice water, extracted with dichloromethane. The organic layer was dried with anhydrous sodium sulphate; crude product was purified by column chromatography. The comparison of the hydroxyl analog and the chloro analog was made in terms of one and two dimensional NMR data and HRMS of the chloroderivative (see SI).
Gymnopalyne A, **3l**: Pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.97 Hz, 1H), 7.74 (dt, J = 7.79, 1.21 Hz, 1H), 7.56 (dt, J = 7.98, 1.16 Hz, 1H), 7.43 (d, J = 7.81 Hz, 1H), 6.78 (s, 1H), 4.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.0, 129.9, 129.5, 125.9, 112.5, 29.71; HRMS–MS: m/e 219.0206, $C_{12}H_7ClO_2$ required Exact Mass.: 218.0135.
For other derivatives see SI.