Tetrahedron Letters 56 (2015) 784–788

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient and convenient copper-free $Pd(OAc)_2$/Ruphos-catalyzed Sonogashira coupling in the preparation of corfin analogues

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ARTICLE INFO

Article history:
Received 19 October 2014
Revised 5 December 2014
Accepted 10 December 2014
Available online 23 December 2014

Keywords:
Sonogashira coupling
3-Chloro-1*H*-isochromen-1-one
$Pd(OAc)_2$/Ruphos
Aqueous conditions
3-(Alkynyl)-1*H*-isochromen-1-ones
Corfin analogues

ABSTRACT

The Sonogashira coupling reaction of 3-chloro-1*H*-isochromen-1-one and terminal alkynes, in the presence of catalytic system-$Pd(OAc)_2$/Ruphos, Et_3N base, and tetrahydrofuran solvent under aqueous conditions, provided novel 3-(alkynyl)-1*H*-isochromen-1-ones in excellent yields. The methodology has also been extended toward natural isochromen-1-ones—corfin analogues.

Introduction

Various strategies have been developed for the synthesis of 3-substituted isochromen-1-ones.[1] Reich et al., have demonstrated the synthesis of methyl 2-(2-(1-oxo-1*H*-isochroman-3-yl)ethynyl)benzoate (Fig. 1), through the lithiation of methyl-2-ethynyl benzoate with LDA, followed by quenching with 2-(carboxymethyl) phenylacetaldehyde.[2]

Moreover, the 3-(2-*R*-ethynyl)-1*H*-isochroman-1-ones, for instance, gymnopalyne A and B[3], were isolated from cultures of a basidiomycete and utilized as key intermediates for the transformation into the alkene and alkyl derivatives, which are nonpeptide HIV Pr inhibitors. Likewise the naturally occurring 3-butylisocoumarins[3b], for instance, corfin, 3′-hydroxycorfin, and analogues were isolated from the roots of *Chamaemelum mixtum*, *Artemisia dracunculus*. Nevertheless; no specific report is accessible for the synthesis of 3-alkenyl-1*H*- and 3-alkynyl-1*H* isochromen-1-ones.

Due to such pervasiveness and eminence considerable efforts have been devoted toward the synthesis of novel 3-(2-*R*-ethynyl)-1*H*-isochromen-1-ones via the Sonogashira coupling strategy.[4] Sonogashira coupling is the most versatile and the easiest method for the synthesis of internal acetylenic compounds involving Pd-catalysis.[5] Since it was discovered by Sonogashira in 1975[6] several modifications have been made in the recent years including a variety of ligands, palladium sources, solvents, amines, and the amount of catalyst load.[7] The most critical modification is the elimination of copper salt in the reaction to evade the in situ generation of copper acetylide side reactions of terminal alkynes to diynes in the presence of oxygen.[8]

Considering the previously stated constrains, in the present investigation of Sonogashira coupling, considerable efforts have been directed to explore an efficient catalytic combination in the synthesis of 3-alkynyl-1*H*-isochromen-1-ones, that is, triphenylphosphine has been superseded with various phosphines to improve the effectiveness of the catalyst. The optimization study demonstrated that the utilization of $Pd(OAc)_2$/Ruphos catalyst, triethylamine as the base and in tetrahydrofuran solvent under aqueous conditions offered noteworthy effectiveness in the synthesis of 3-(2-*R*-ethynyl)-1*H*-isochromen-1-ones.

In our continued interest in the synthesis of different 3-substituted isocoumarins[9–14] and related compounds, the use of palladium catalysis has been attempted in the formation of highly functionalized and novel 3-(2-*R*-ethynyl)-1*H*-isochromen-1-ones. The chemistry of 3-alkynyl isochromen-1-ones synthesis is a totally new idea and it requires proper optimization for the

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http://dx.doi.org/10.1016/j.tetlet.2014.12.059
0040-4039/

formation of desired internal acetylenic compounds in good yield. In our preparatory study, the optimization of Sonogashira coupling was done using 3-chloro-1*H*-isochromen-1-one, **1a** with phenyl acetylene, **2a** as the model reaction (Scheme 1).

At first, the reaction was done utilizing $Pd(OAc)_2$ as the catalyst, Na_2CO_3 as the base and THF or dioxane as the solvent by heating the reaction mixture at 80 °C for 1 h. These conditions failed to offer the desired product, **3a** (Table 1, entries 1 & 2). Further, the Sonogashira reaction was explored using $Pd(OAc)_2$ catalyst, triphenyl phosphine ligand, triethyl amine as the base, and THF or dioxane as the solvent with heating at 80 °C for 1 h. The tested condition provided product in 20% and 25% yields, respectively (Table 1, entries 3 & 4).

With this result in hand, the reaction condition was changed utilizing $Pd(OAc)_2$/CuI catalyst system, triethylamine base and in THF solvent which however provided a 50% conversion to the desired product (Table 1, entry 5). The reactions when done under aqueous condition demonstrated 100% conversion, but, with various impurities as observed by TLC (Table 1, entry 6). The temperature variations have likewise been explored (Table 1, entry 7). The above initial investigations did not move ahead to provide pure products and it was hard to isolate the pure product with good quality.

To develop a suitable catalytic combination and to overcome the above difficulties, significantly more attempts of comprehensive screening of different ligands were taken up, as presented in

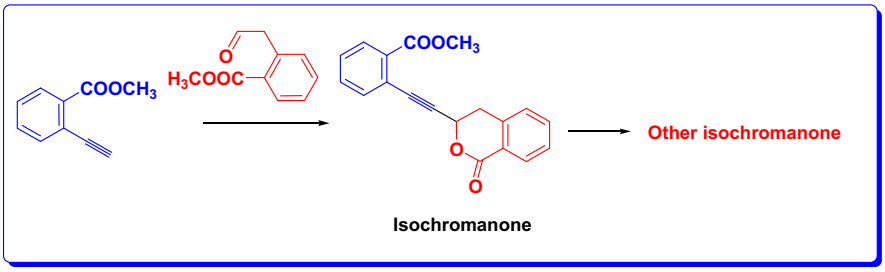
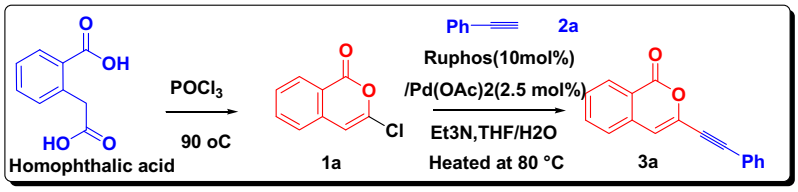


Figure 1. Isochromanones.



Scheme 1. Sonogashira coupling of 3-chloro-1*H*-isochromen-1-one, **1a** with phenylacetylene, **2a**.

Table 1
Sonogashira coupling of 3-chloro-1*H*-isochromen-1-one with phenyl acetylene: optimization of the reaction conditions[a]

S. No.	Catalyst	CuI (mol %)	Ligand	Solvent	Conv. (%)	Yield (%)
1	$Pd(OAc)_2$	—	—	THF	NR[b]	—
2	$Pd(OAc)_2$	—	—	Dioxane	NR[b]	—
3	$Pd(OAc)_2$	—	PPh_3	THF	20	—
4	$Pd(OAc)_2$	—	PPh_3	Dioxane	25	—
5	$Pd(OAc)_2$	10	—	THF[c]	50	42
6	$Pd(OAc)_2$	10	—	THF + H_2O[c]	100	—
7	$Pd(OAc)_2$	10	—	THF + H_2O[d]	10–20	—
8	$Pd(OAc)_2$	10	Ruphos	THF + H_2O[d]	10	—
9	$Pd(OAc)_2$	—	Ruphos	THF +H_2O	100	83
10	$Pd(OAc)_2$	—	Sphos	THF + H_2O	70–80	69
11	$Pd(OAc)_2$	—	Xanthphos	THF + H_2O	25–30	20
12	$Pd(OAc)_2$	—	BINAP	THF + H_2O	35–40	30
13	$Pd(OAc)_2$	—	dppb	THF + H_2O	30–40	25
14	$Pd(OAc)_2$	—	dppf	THF + H_2O	30–40	23
15	$Pd(OAc)_2$	—	Cy_3P	THF + H_2O	35–40	30
16	$Pd(OAc)_2$	—	$(n\text{-Bu})_3P$	THF + H_2O	40–50	36
17	$Pd(OAc)_2$	—	Oxydiphos	THF + H_2O	80–90	76
18	$Pd(OAc)_2$	—	Xphos	THF + H_2O	80–90	72
19	$PdCl_2(PPh_3)_2$	—	Oxydiphos	THF + H_2O	80–90	71
20	$PdCl_2(PPh_3)_2$	—	Xphos	THF + H_2O	80–90	64
21	$PdCl_2(PPh_3)_2$	—	Ruphos	THF + H_2O	80–90	79
22	$PdCl_2(PPh_3)_2$	—	Sphos	THF + H_2O	80–90	63

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), base is Et_3N (2 equiv) unless otherwise stated, Pd catalyst (2.5 mol %), ligand (10 mol %), THF (5 mL), degassed water (0.5 mL) at 80 °C for 1–5 h.
[b] Na_2CO_3.
[c] 1.5 h.
[d] 20–25 °C.