EFFECTIVE SYNTHESIS OF SOME NOVEL 7,8-SUBSTITUTED COUMARINS THROUGH HECK REACTION AND SONOGASHIRA’S COUPLING REACTIONS

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Abstract- In this paper we would like to report the synthesis of medicinally active 7,8-substituted coumarins were attempted by using the Heck reaction of iodocoumarin with olefin to gave product 7,8-substituted chromenyl maleate is accomplished by the use of an organ palladium catalyst, and a base. Sonogashira coupling reaction of 8-iodo umbelliferone with propargyl alcohol to gave product coumarin substituted propargyl alcohol by using freshly prepared tetrakis(triphenylphosphine)palladium catalyst and copper (I) iodide in dry THF was carried out. A carbon-carbon single bond formed in both the coupling reactions and good yields are obtained.

Keywords- coumarins, Heck reaction, Sonogashira coupling, organ palladium catalyst copper (I) iodide, THF.

I. INTRODUCTION

Coumarin 1 (benzo-α-pyrene) and flavonoid 2 (benzo-γ-pyrones) are members of benzopyrone systems, which are found in many vegetables, seeds, fruits like bilberry, nuts, coffee, tea, cinnamon bark oil and wine. Synthetic coumarins are widely used as aroma chemicals because of their odour strength, stability to alkali and relatively cheap price. Applications of coumarins include use as a sweetener and fixative (in perfumes), fragrance enhancers (for natural essential oils), blenders (in soaps and detergents), aroma enhancers (in tobacco) and for imparting pleasant odours to industrial products. Variety of flavonoids show in vitro antibacterial, antifungal and antiviral activities. The flavonol glycosides were used for the treatment of cold, fever, headache, cough.

The 7, 8-disubstituted coumarins are also found abundantly in nature. Some of them are shown in Figure 3. The 7, 8-substituted coumarin 13 was isolated from the leaves of Galipea panamensis. It was tested against axenic amastigote forms of Leishmania panamensis and displayed EC₅₀ of 10.5 μg/mL. It also displayed cytotoxicity (IC₅₀) at concentrations of 33.0 μg/mL on human promonocytic U-937 cells.

Figure-1
II. RESULTS AND DISCUSSION

The Heck reaction of iodocoumarin 17 with olefin 19 was carried out using \((o\text{-tolyl})\) triethylamine, and \(\text{Pd(OAc)}_2\) in DMF. After the usual workup and column chromatographic separation, two products were obtained in 91% yield. Major product was in 91% and minor was in 9% yield.

Thus, in the Heck coupling reaction, (Scheme-1) the expected product 20 was not obtained and an unreported compound 21 was resulted as a major product along with compound 22 as a minor product also de-iodinated 15, 18. The products are widely used for the treatment of disease like cancer 16-20.

Sonogashira coupling reaction (Scheme-2) of 8-iodo umbelliferone 17 with propargyl alcohol 23 using triethylamine, freshly prepared tetrakis(triphenylphosphine)palladium catalyst and copper (I) iodide in dry THF was carried out. It gave product 24 in 70% yield after chromatographic purification. Thus, coumarin substituted propargyl alcohol 24 was synthesized in this reaction.

The palladium cycle is similar to the Heck reaction i.e. oxidative addition, transmetallation, and reductive elimination. Copper cycle is also involved in the same mechanism. In the presence of base, the formation of a \(\pi\)-alkyne complex, makes the terminal proton on the alkynes more acidic. This leads to the formation of the copper acetylide and which reacts with the palladium intermediate, with regeneration of the copper halide.

III. CONCLUSION

All the products are formed in Heck reaction and Sonogashira’s coupling (Scheme-1) and (Scheme-2) reactions are furthered confirmed by \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR and HRMS studies. All the products are monitored by TLC and isolated by GC.
IV. EXPERIMENTAL SECTION

8-Iodo-7-methoxycoumarin (17)

A mixture of 8-iodoumbelliferone (600 mg, 2.08 mmol), methyl iodide (0.25 ml, 4.1 mmol, 2.0 equiv.) and anhydrous potassium carbonate (574 mg, 4.1 mmol, 2.0 equiv.) in anhydrous acetone (20 ml) was heated to reflux for 5 h. Dilute aqueous hydrochloric acid solution (5 ml) followed by water (20 ml) were added. The mixture was extracted with dichloromethane (3x20 ml), and the combined organic extracts were washed with brine (60 ml), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂; EtOAc/n-hexane, 1:3) to give the title compound as pale cream coloured needles (520 mg, 82%). M.p. 160°C.

1H NMR (300 MHz, CDCl₃): δ 4.02 (s, 3H) 6.26-6.27 (d, J = 9.53 Hz, 1H) 6.80-6.80 (d, J = 8.58 Hz, 1H) 7.43-7.46 (d, J = 8.58 Hz, 1H) 7.57-7.62 (d, J = 9.54 Hz, 1H).
13C NMR (125 MHz, CDCl₃): δ 56.99, 76.04, 107.37, 113.72, 113.92, 129.03, 143.02, 155.03, 160.47, 161.67.
HRMS (ESI): m/z calcd for C₁₀H₈IO₃ (M+H)+, 302.9513; found, 302.9514.

Dimethyl methylmaleate (19)

To a solution of citraconic anhydride (4.48 g, 40 mmol) in methanol (40 mL) was added H₂SO₄ (4 mL) and mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated using rotary evaporator under vacuum. The residue was diluted with water and extracted
with ethyl acetate. The combined organic layer was washed with aqueous solution of NaHCO₃, brine, and dried over Na₂SO₄. Concentration of organic layer in vacuum gave pure diester as thick oil in 75%.

**Dimethyl 2-((7-methoxy-2-oxo-2H-chromen-8-yl)methyl)maleate (21)**

A mixture of iodide 17 (0.2 g, 0.66 mmol), dimethyl methylmaleate 19 (0.52 g, 3.28 mmol), (o-tolyl)₃P (0.1 g, 0.32 mmol) and triethyl amine (1.01 mL, 7 mmol) in DMF (10 mL) was degassed at 0 °C. Then, Pd(ACO)₂ (0.025 g, 0.11 mmol) was added and the resulting mixture was released at the same temperature. The resulting reaction mixture was heated at 90 °C with vigorously stirring. The reaction was monitored by TLC. After the total consumption of the starting material, the mixture was passed through a short celite pad. The precipitate on the filter was washed with a small volume of DMF and the filtrates were combined and diluted with CHCl₃. The organic phase was washed with H₂O, dried over Na₂SO₄ and separated by column chromatography using silica gel using pet ether-ethyl acetate as eluent to give product 21 as a brownish solid having M. p. 79 °C (91%) along with 22 as a brownish solid having M. p. 82 °C (9%).

**7-methoxy-2H-chromen-2-one (22)**

To a stirred solution of the iodide 17 (0.5 g, 1.65 mmol) in degassed THF (20 ml) was added triethylamine (4.8 mL, 3 ml per mmol). The tetrakis(triphenylphosphine)palladium (0.38 g, 20 mol%)
was added further propargyl alcohol (0.14 mL, 0.13 g, 2.48 mmol) was added. The mixture was refluxed under nitrogen for 1 h. Then copper (I) iodide (0.06 g, 20 mol%) was added. Refluxing was continued for 18 h, then the mixture was cooled to room temperature and treated with water (10 ml). Stirring was continued for 4 h then the mixture was separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic solutions were washed with water (15 mL) and brine (15 ml) then dried over Na₂SO₄ and concentrated. The desired product was purified by column chromatography to get light yellow solid compound in 70%. M. p. 104°C.

\[ \text{HO} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{O} \]

\[ ^{1} \text{H NMR (300 MHz, CDCl}_3\text{: }\delta \text{ 3.97 (s, 3H), 4.46 (t, } J = 6.20 \text{ Hz, 1H), 4.57-4.59 (d, } J = 6.20 \text{ Hz, 2H), 6.26-6.29 (d, } J = 9.54 \text{ Hz, 1H), 6.86-6.90 (d, } J = 9.06 \text{ Hz, 1H), 7.42-7.45 (d, } J = 9.54 \text{ Hz, 1 H), 7.65-7.69 (d, } J = 9.54 \text{ Hz, 1 H).} \]

\[ ^{13} \text{C NMR (125 MHz, CDCl}_3\text{: }\delta \text{ 50.84, 56.24, 73.78, 99.28, 100.90, 107.04, 112.50, 113.23, 128.31, 143.11, 155.26, 160.19, 162.89.} \]

HRMS (ESI): m/z calcd for C₁₃H₁₀NaO₄ (M+H)+, 253.0471; found, 253.0475.

V. CONCLUSION

We have developed a convenient and simple protocol for the synthesis of coumarin derivatives through heck and sonogashiras coupling which were most significant in medicinal field and possess an excellent biological activity.

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