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Copper(II) Salt Catalyzed Coupling Strategy Towards Synthesis of Substituted Dibenzopyranones

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Copper salts are environmentally friendly and less expensive as compared to other transition metal salts. These salts have historically been used for carbon-carbon cross-coupling reactions. In present work, we adopted $CuSO_4$ catalyzed C-C coupling reactions in presence of base to obtain series of substituted dibenzopyranone derivatives.

Keywords: Copper(II), Catalysis, Coupling, Synthesis, Dibenzopyranones.

INTRODUCTION

Coupling reactions particularly catalyzed by transition metal have received massive interest by virtue of its applicability [1-6]. Before 150 years, one of the first copper-mediated coupling reaction was developed by Glaser [7] featuring the dimerization of terminal acetylenes. Ullmann and Bielecki [8] paved the way for the copper-mediated synthesis of biaryls starting from aryl bromides in roughly year 1901. Copper-based catalysts for various coupling reactions are found to be more attractive due the lower cost and environmental factors associated with it [9-12]. In fact, acetylenes and halides as partners in Sonogashira reaction [13] employs catalytic amount of Pd(0) and Cu(I). Towards advancing catalysis as a science, Buchwald *et al.* contributed on Cu-catalyzed cross-coupling reactions by amalgmating chelating ligands [14-16]. Mechanistically, use of ligands in such processes lower the activation energy of the metal catalyst and moderates the coupling reaction in a much faster pace. It has recently been reported that, in the presence of light and a copper(I) catalyst, nitrogen nucleophiles undergo C–N coupling with alkyl halides under mild conditions. Moreover, it has also been established that photo induced, copper-catalyzed alkylation can also be applied to C–C bond formation [17a]. Shi *et al.* [17b] have accomplished a synthesis of dibenzopyranones but by using Pd(II) and Cu(II) dual catalytic system. Shi's group has also enlisted several other ways of synthesizing this scafold. In present work, we used a substrate that does not require in ligand yet extremely effective in coupling reaction towards the synthesis of dibenzopyranones. The dibenzopyranone is found in many natural products *e.g.* fruits, herbs and vegetables. Myriad of methods reported towards synthesis of dibenzopyranones, notably, in 2002, Abbott Laboratories manage to synthesize glucocorticoid receptor A-224817.0 through Negishi cross coupling but the disadvantages associated of these methods include poor process efficiency, multistep sequence and intensive purification of the intermediates. Here we report $CuSO_4$ catalyzed C-C coupling reactions in presence of base to obtain series of substituted dibenzopyranone derivatives with mechanistic understanding as shown in Fig. 1.

EXPERIMENTAL

Typical procedure for the synthesis of the targeted compounds **3**(**a**-**e**) is described. Uncorrected open capillaries Toshniwal melting point apparatus has been used to record the melting points. Brucker Avans DRX 300 (300 MHz, FT NMR) spectrometer using TMS as internal standard has been used to record the ^{1}H NMR and the chemical shift are reported in δ (ppm) scale and the coupling constants are reported in Hz. JEOL-JMSD 300 instruments fitted with a direct inlet system were employed to run electron impact (EIMS) mass spectra. Elemental analyzer EA-1108 was used in elemental analysis and results were within ± 4 % of theoretical values. The purity of the products was checked on Precoated silica gel 60 F_{254} or aluminium oxide 60 F_{254} TLC plates were used to check the purity and the iodine vapours spray were used to visualize the spots.

3,8-Dihydroxy-9-methoxy-6*H*-benzo[c]chromen-6-one (3a): Resorcinol (550 mg, 5 mM) was added to a solution of

methyl 2-bromovanillic acid (598 mg; 2.42 mM) in aqueous sodium hydroxide (8 %, 2.5 mL). After refluxing the reaction mixture at 120 °C by using in an oil bath for 45 min aqueous copper sulfate solution (5 %, 1 mL) was added and the reaction mixture was refluxed for another 15 min. Precipitated product was filtered off after cooling and washed with water (1 mL × 3), dried. Crystallization of product was achieved by using acetic acid (2 mL)- methanol (5 mL) to obtain157 mg brown amorphous solid. Yield, 61 %, m.p., 288 °C, ^{1}H NMR ($CDCl_3$, δ ppm): 3.91 (s, 3H, OCH_3), 6.73 (d, 1H, H^4, J = 3.0 Hz), 6.82 (dd, 1H, H^2, J = 12.0, 6.0 Hz), 7.40 (s, 1H, H^{10}), 7.50 (s, 1H, H^7), 7.90 (d, 1H, H^1, J = 12.0 Hz). Mass: $C_{14}H_{10}O_5$; 258 (M^+) 243, 219, 215, 187, 131, 91, 69.

3-Hydroxy-8,9-dimethoxy-6*H*-benzo[c]chromen-6-one (3b): Compound **3b** was prepared by similar procedure as described for **3a**. In this particular synthesis, 4,5-dimethoxy-2-bromobenzoic acid (568.98, 2.18 mM) and resorcinol (550 mg; 5 mM) were used. Weight: 142 mg, Yield: 52 % m.p. > 280 °C, ^{1}H NMR ($CDCl_3$, δ ppm): 3.85 (s, 3H, 8-OCH_3), 3.98 (s, 3H, 9-OCH_3), 6.71 (d, 1H, H^4, J = 3.0 Hz), 6.80 (dd, 1H, H^2, J = 9.0, 3.0 Hz), 7.5 (s, 1H, H^{10}), 7.6 (s, 1H, H^7), 8.16 (d, 1H, H^1, J = 15.0 Hz), Mass: $C_{15}H_{12}O_5$; 272 (M^+), 258, 228, 214, 158, 121.

8-(Benzyloxy)-3-hydroxy-9-methoxy-6*H*-benzo[c]-chromen-6-one (3c): Compound **3c** was prepared by similar procedure as described for **3a**. In this particular synthesis, 4-benzyloxy 3-hydroxy 8-methoxy 2-bromobenzoic acid (630 mg; 2.18 mM) and resorcinol (550 mg; 5 mM) were used. Weight: 41 mg; Yield, 52 %. ^{1}H NMR ($CDCl_3$, δ ppm): 3.91 (s, 3H, OCH_3), 5.49 (s, 2H, OCH_2), 6.87 (d, 1H, H^4, J = 3.0 Hz), 6.95 (dd, 1H, H^2, J = 4.5, 1.5 Hz), 7.49-7.69 (m, 7H, H^7, H^{10} and Ar-H), 7.93 (s, 1H, H^7), 8.28 (d, 1H, H^1, J = 12.0 Hz), Mass: 272 (M^+), 258, 228, 214, 158, 121.

3-Hydroxy-9-methoxy-8-[2-(pyrrolidin-1-yl)ethoxy]-6*H*-benzo[c]chromen-6-one (3d): Compound **3d** was prepared by similar procedure as described for **3a**. In this particular synthesis, 2-bromo 5-methoxy 4-pyrrolidinoethoxy benzoic acid (826 mg; 2.12 mM) and resorcinol (550 mg; 5 mM) were used. The product was crystallized by using methanol (2 mL)-water (0.5 mL). Weight: 170 mg; Yield, 47.8 %; m.p., 196 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.70-1.80 (m, 4H, $(CH_2)_2$ of pyrrolidine), 2.50-2.57 (m, 4H, $N(CH_2)_2$ of pyrrolidine), 2.98 (t, 2H, NCH_2, J = 9.0 Hz), 3.98 (s, 1H, OCH_3), 4.33 (t, 2H, OCH_2, J = 3.0 Hz), 6.76 (d, 1H, H^4, J = 15.0 Hz), 6.85 (dd, 1H, H^2, J = 4.5, 1.5 Hz), 7.53 (s, 1H, H^7), 7.64 (s, 1H, H^{10}), 8.18-8.22 (m, 1H, H^1), 9.13 (s, 1H, OH), Mass: $C_{20}H_{21}O_5N$; 355 (M^+), 307, 289, 242, 154, 136.

3-Hydroxy-8-methoxy-9-piperidinoethoxy dibenzo-[b,d]pyran-6-one (3e): Compound **3e** was prepared by similar procedure as described for **3a**. In this particular synthesis, 1 g (830 mg; 2.18 mM) 2-bromo 5-methoxy 4-piperidinoethoxy benzoic acid and resorcinol (550 mg, 5 mM) were used. The product was crystallized by using methanol (2 mL) water (0.5 mL). Weight: 184 mg; Yield, 49.8 %; m.p., 205 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.4-1.5 (m, 6, $(CH_2)_3$ of piperidine ring), 2.4-2.7 (m, 4H, $N(CH_2)_2$ of piperidine ring), 2.74 (t, 2H, NCH_2, J = 6.0 Hz), 3.77 (s, 3H, OCH_3), 4.33 (t, 2H, OCH_2, J = 6.0 Hz), 6.73 (d, 1H, H^4, J = 6.0 Hz), 6.82 (dd, 1H, H^2, J = 12, 9.0 Hz), 7.5 (s, 1H, H^7), 7.71 (s, 1H, H^{10}), 8.21 (dd, 1H, H^2, J = 12, 9.0 Hz), Mass: $C_{21}H_{23}O_5N$; 369 (M^+), 149, 121, 91, 55.

RESULTS AND DISCUSSION

The C-H activation is one of the most fascinating areas in transition metal catalyzed syntheses. Here in our efforts, aryl C-H activation is being effective due to the fact that phenolic hydroxy functionality is present at *para* position to the C-C bond forming carbon in one of the aromatic rings. Eventually, compounds **3**(**a**-**e**) have been synthesized by reacting substituted *ortho*-bromobenzoic acids [**1**(**a**-**e**)], with resorcinol (**2**) in aqueous alkaline medium in presence of copper(II) sulfate. Substrates **1**(**a**-**c**) are substituted with relatively less bulky protecting groups whereas substrates **1d** and **1e** are fully decorated with ethyl pyrrolidine and ethyl piperidine. As shown in Fig. 1, the proposed mechanism operates through Cu(III) species [18], resulted after oxidative insertion of Cu(II) across aryl halide carbon halogen bond in **2a**. Strategically placed phenolic hydroxy group helped in metalation thereafter reductive elimination afforded the desired product. As a result, Cu(I) species possibly gets oxidized in presence of aerial oxygen to Cu(II) to maintain the catalytic cycle as shown in Fig. 1.

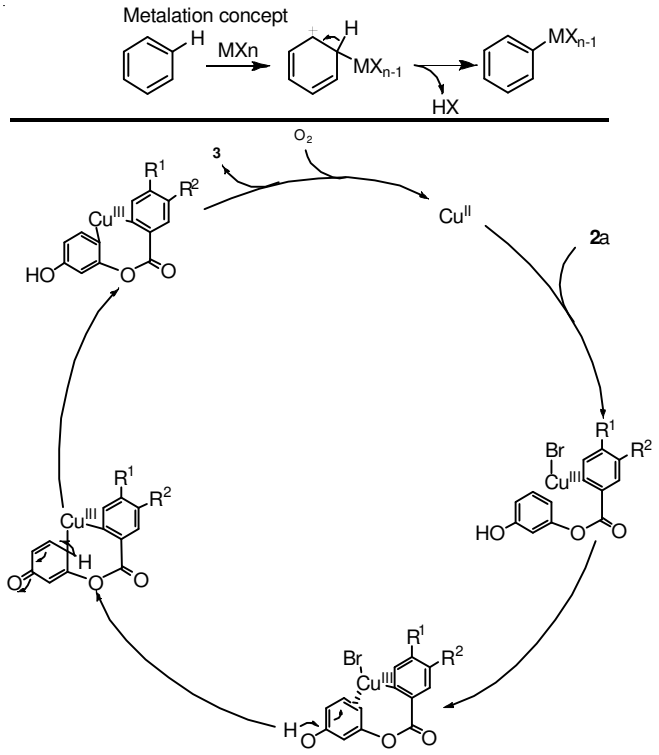
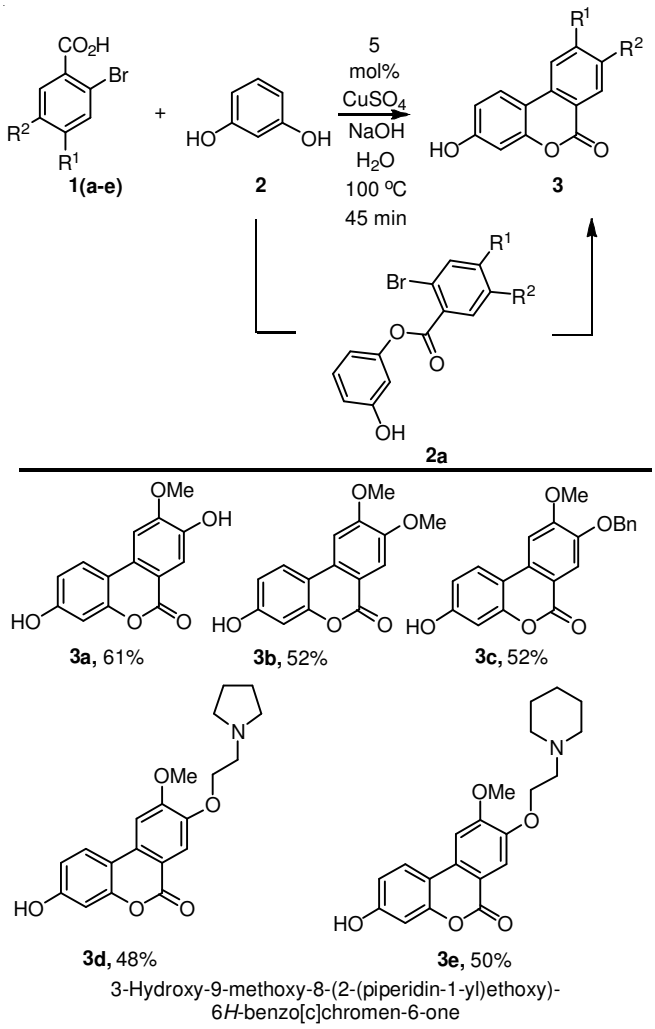


Fig. 1. Proposed mechanism for Cu(II) catalyzed synthesis of substituted dibenzopyranone derivatives

There were number of compounds **3**(**a**-**e**), substituted dibenzopyranone derivatives synthesized. Synthetic strategy involved 2-bromovanillic acid derivatives and resorcinol in presence of sodium hydroxide solution in water under refluxing conditions. The substrate variation is maintained along with R^2 substituents in 2-bromovanillic acid derivatives. Substrate **1a** has only phenolic hydroxyl functionality that would have helped C-Br bond present at *para* position to take

part in oxidative insertion event quite effectively due to inductive effective leading to offer higher yield of the product (61 % **3a**). Other two substrates **1b** and **1c** have similar substituents (*e.g.* –OMe and –OBn) would have followed similar course of C-C bond forming events as substrate **1a** would have gone through. The yields for corresponding products [**3b** and **3c** (52 and 52 %)] are slightly lower than that of **3a**. Last two substrates are fully functionalized with side chains containing pyrrolidine and piperidine bases. Non-bonding lone pair of electrons at nitrogen of these bases would have mortgaged the reactivity up of Cu(II) to certain extent during oxidative insertion as a crucial event leading to formation of the products with lesser yields [**3d** and **3e** (48 % and 50 %)] than the other products (**3a**, **3b** and **3c**). In order to believe that this reaction is being progressed in a catalytic fashion, the role of dissolved can't be ruled out. Mechanistically, we reasoned that dissolved oxygen in water acts as oxidant in order to establish the catalytic cycle. This process affords product with yield ranging from 48 to 61 %.

Various *ortho*-bromobenzoic acids, used in the **Scheme-I** were in turn prepared by known literature methods starting from simple starting materials [19a-c].



Scheme-I: Synthesis of substituted dibenzopyranone derivatives

Conclusion

A series of series of substituted dibenzopyranone derivatives have been synthesized by using Cu(II) salt which is environmentally friendly and less expensive as compared to other transition metal salts. Further expansions of this strategy to make medicinally relevant molecules are under progress.

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