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ARTICLE

Hydroxyl directed C-arylation: synthesis of 3-hydroxyflavones and 2-phenyl-3-hydroxy pyran-4-ones under transition-metal free conditions

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An efficient, transition-metal free and direct C-arylation of 3-hydroxychromone moieties in presence of base, air as oxidant and arylhydrazines as arylating agent to furnish highly biologically active flavonols or 3-hydroxyflavones has been developed. We have further extended our methodology for the C-arylation of 5-hydroxy pyran-4-one moiety. The role of free hydroxyl group towards C-arylation has been delineated.

Flavonols or 3-hydroxyflavones (3-HF, **I**), a unique class of flavonoid are ubiquitous in nature and are present in various plant families.[1] These have been found to be highly biologically active molecules (Figure 1).[2] Compound **II** was isolated[3] from EtOAc extract of the leaves and twigs of *Pistacia atlantica* (Anacardiaceae) and shows antiplasmodial activity against *Plasmodium falciparum* strain K1 (chloroquine and pyrimethamine resistant) with IC_{50} value of 3.4 µM. The alcoholic extract of the aerial parts of *Nervili fordii* (Orchidaceae) afforded compound **III** which was found to be active (IC_{50} 16.8 µM) against NO production in lipopolysaccharide-stimulated murine macrophage (RAW264.7).[4] Macaranone A **IV** active against (IC_{50} 6.9 µM) human liver cancer cell line (HepG2) was isolated from EtOAc extract of the leaves of *Macaranga sampsonii* (Euphorbiaceae).[5] Silychristin **V** and silybin **VI** found in the fruits of *Silybum marianum* were found to possess radical scavenging and inhibition of lipoperoxidation activities.[6] Saggenone D **VII** was isolated from the root bark of white mulberry tree, *Morus alba* L. (Moraceae) and shows inhibitory activities against influenza A virus and *Streptococcus pneumoniae* with IC_{50} values of 3.1 µM and 31.6 µM respectively.[7] Recently, flavonols based Ru(II) metal drugs have been developed as anticancer agents.[8]

In recent years, C–H functionalization or activation to form C–C bond *via* cross-coupling reactions has been of great interest for the synthesis of various biologically active aromatic compounds. The most favoured method for C–H functionalization/activation being the use of transition-metal catalysed reactions.[9] However, transition-metal catalysed reactions have their own limitations such as high cost of the catalysts and harsh reaction conditions etc.[10] The synthesis of 3-hydroxyflavones is presently being carried out using Algar-Flynn-Oyamada (AFO) reaction,[11] which requires longer reaction time and the product is formed in less yield. Therefore, development of a reaction for the synthesis of 3-hydroxyflavones using transition-metal free C-arylation of 3-hydroxychromones is highly desirable.

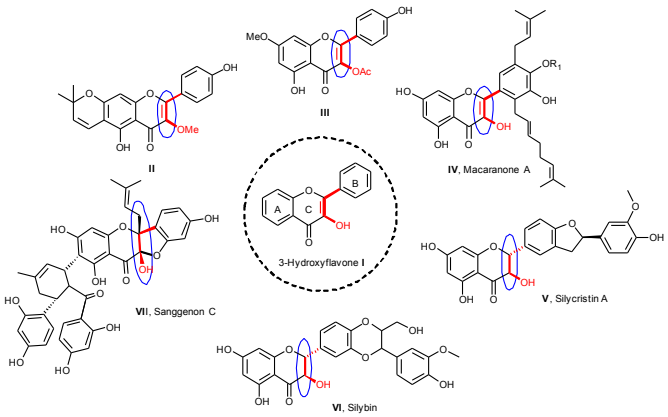

Figure 1 Representative bioactive compounds containing the 3-hydroxyflavones (3-HF)

Arylating reagents such as reactive aryl radical species formed *via* denitrogenation of arylhydrazines[12] for the C-arylation could be an alternative method to transition-metal catalysed C-arylation over other arylating sources.[10,13] It is reported that arylhydrazines furnish arenes with the release of N_2 under oxidative conditions however, in the presence of base, formation of arenes is much faster.[13b] We envisioned that direct C-arylation of 3-hydroxychromone moiety could be achieved using arylhydrazines as aryl radical source under basic condition. Initially, we reacted chromone **1a**, our model substrate with *p*-tolyl hydrazine hydrochloride **2a** in DMSO with K_2CO_3 as base at room temperature in open flask. It was presumed

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Electronic Supplementary Information (ESI) available: Complete characterization data of all the compounds synthesized and their spectra. See DOI: 10.1039/x0xx00000x

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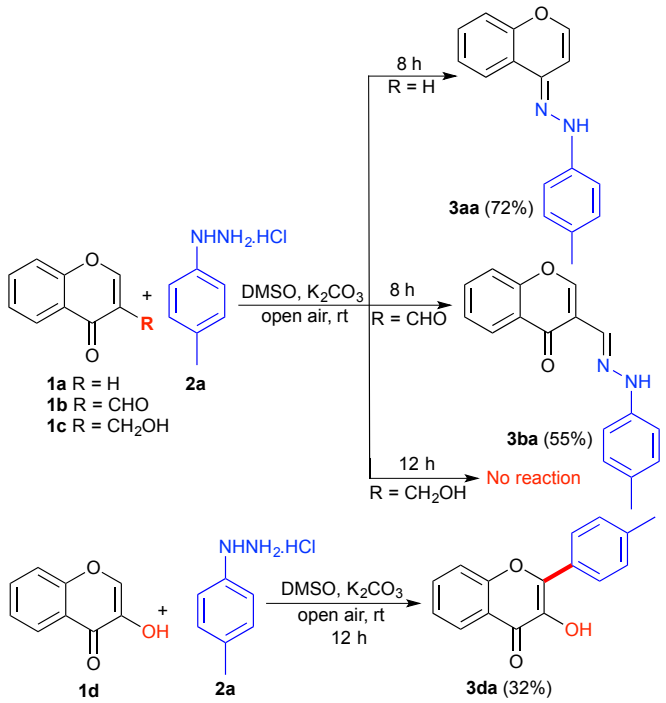
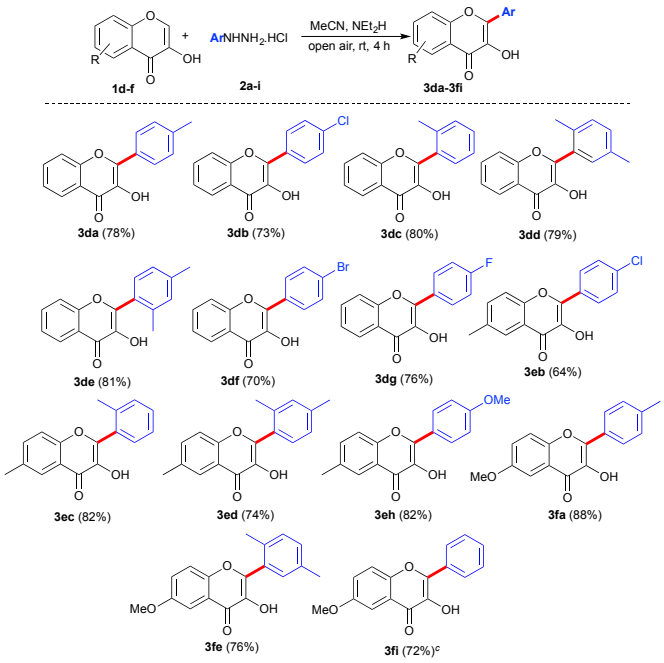
that the aryl radical would form and react with the double bond between C-2,3 to afford the corresponding C-arylated product (Scheme 1). The reaction however, resulted in the formation of hydrazone **3aa** rather than the expected C-arylated product. The formation of hydrazone **3aa** suggests that the hydrazine **2a** immediately reacted with the carbonyl of chromone before aryl radical could be formed under the basic reaction condition. We opined that the double bond between C-2,3 may not be reactive, as compared to the carbonyl functionality of the chromone hence we introduced a formyl group at C-3. However, the reaction of 3-formyl chromone **1b** with **2a** under the same reaction conditions also lead to the formation of hydrazone **3ba**. We also studied the reaction with compound **1c** bearing a hydroxymethyl group at the C-3 position.[14] However, even after 12 h, neither traces of the C-arylated product nor the hydrazone formation was observed instead starting material **1c** was recovered unreacted while hydrazine **2a** forms an inseparable mixture. The relatively less reactivity of compound **1c** could be attributed to the strong six-membered intramolecular hydrogen bonding. These observations led us to reason for a suitable group, which would direct C-arylation. We then studied the reaction of 3-hydroxychromone **1d**[14] with **2a** under the basic condition presuming that hydroxyl group at C-3 may enhance the reactivity of the double bond. Indeed, our surmise was proved correct with the formation of C-2 arylated product **3da** in 32% yield (Scheme 1).



Scheme 1 Primary studies on C-arylation of differently substituted chromones.

With the desired product in hand, we optimized our reaction conditions by varying base, solvent, oxidant and equivalence of hydrazine on the outcome of this reaction (Table S1, see SI). Optimized condition was obtained (Table S1, entry 7, see SI) when diethyl amine (3.5 equiv.) and 4-tolylhydrazine hydrochloride (1.5 equiv.) corresponding to 3-hydroxychromone **1d** were reacted, respectively. Having optimized the reaction conditions for the C-2 arylation of 3-hydroxychromone **1d**, we then studied the scope and generality of this developed methodology by reacting various 3-hydroxychromones **1d**-**f** with arylhydrazines **2a**-**i** to furnish flavonol **3da**-**3fi** (Table 1). Reaction of arylhydrazine having electron-donating groups such as methyl, dimethyl and methoxy furnished 3-hydroxyflavones in very good yields whereas arylhydrazines possessing electron-withdrawing groups such as chloro **2b**, bromo **2f** or fluoro **2g** afforded the desired product in good yields. It is pertinent to mention here that phenylhydrazines bearing halides such as chloro **2b**, bromo **2f** or fluoro **2g** were well tolerated by this methodology and can be further utilized for synthesis of hybrid molecules. However, reaction of 3-hydroxychromones **1d**-**f** with arylhydrazines bearing strong electron-withdrawing groups such as 4-CN, 3-NO_2 or 4-NO_2 didn't furnish any C-arylated product and the starting materials 3-hydroxychromones remained unreacted (Scheme 2).

Table 1 Substrate scope[a,b]



[a]Reaction conditions: 3-Hydroxychromone **1d**-**f** (0.25 mmol), **2a**-**i** (0.375 mmol, 1.5 equiv.), diethyl amine (0.875 mmol, 3.5 equiv.), in MeCN (3 mL) at rt under open air; [b]Isolated yield of pure product with respect to **1d**-**f** (in parenthesis); [c]Phenyl hydrazine (**2i**) used as free base, diethyl amine (0.625 mmol, 2.5 equiv.).

After studying the C-arylation reactions of 3-hydroxychromones **1d**-**f**, we further wished to investigate the scope and generality of this methodology on differently substituted pyran-4-one moiety. In this regard, kojic acid **4** ideally suits our requirement as it has a core structure of pyran-4-one moiety bearing suitably oriented hydroxyl as well as hydroxymethyl group as substituents on two different double bonds (Figure 2). Recently, the 2-arylated thio pyrone based Ru(II) drugs have also been reported as cytotoxic agents which can be easily derived from C-arylated kojic acid.[15]

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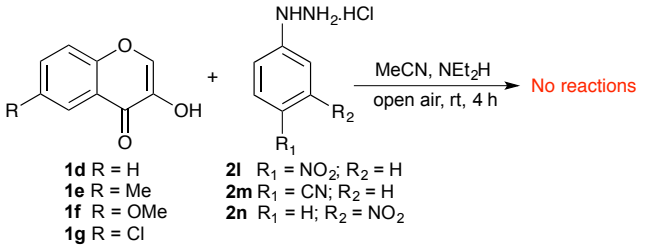


Scheme 2 C-arylation reactions of substituted 3-hydroxychromones with various electron-withdrawing substituents.

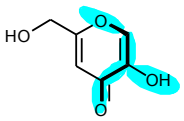
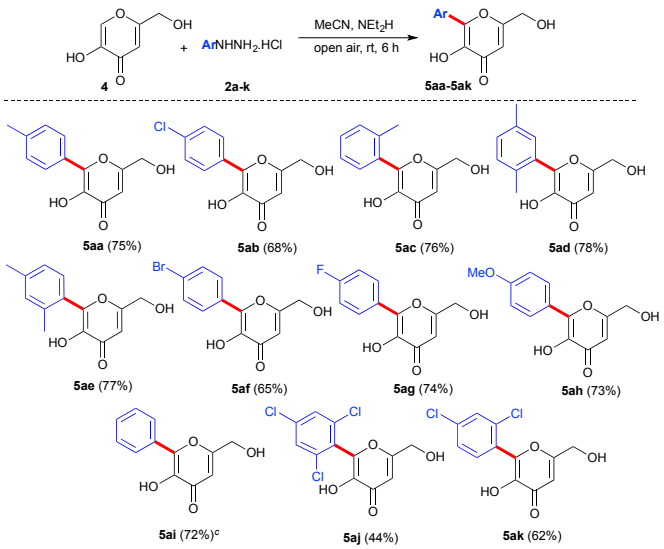


Figure 2 Structure of kojic acid **4**.

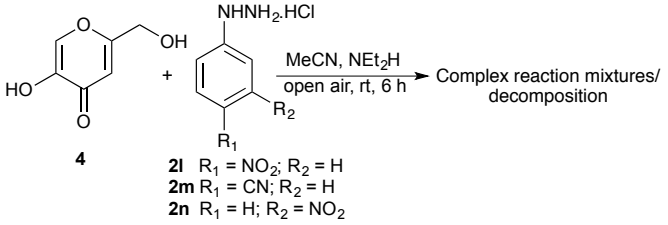
We carried out C-arylation of kojic acid **4** with various arylhydrazines **2a-k** to synthesize C-arylated kojic acid derivatives **5a**-**5k**. Interestingly, all the studied arylhydrazines **2a**-**k** on reaction with kojic acid **4** furnished C-arylated products in very good yields (Table 2).

Table 2 Substrate scope[a,b]



[a]Reaction conditions: Kojic acid **4** (0.25 mmol), **2a-k** (0.375 mmol, 1.5 equiv.), diethyl amine (0.875 mmol, 3.5 equiv.), in MeCN (3 mL) at rt under open air; [b]Isolated yield of pure product with respect to **4** (in parenthesis); [c]Phenyl hydrazine (**2i**) used as free base, diethyl amine (0.625 mmol, 2.5 equiv.).

The product yield pattern was also found to be in tandem with 3-hydroxychromone when reacted with arylhydrazines bearing electron-donating and electron-withdrawing groups, respectively. However, reaction of kojic acid **4** with arylhydrazines bearing strong electron-withdrawing groups such as 4-CN, 3-NO_2 and 4-nitro didn't furnish any C-arylated product instead a complex mixture of products or decomposition of reaction mixtures was witnessed (Scheme 3).



Scheme 3 C-arylation reactions of kojic acid **4** with various electron-withdrawing substituents.

Next, we turned our attention towards the role of hydroxyl group present on chromone on the course of C-arylation reaction as observed in Scheme 1, that why only in the presence of hydroxyl group C-arylation takes place. In this context, we protected the free hydroxy group of **1d** as -OMe **1g**, -OBn **1h** or -OPMB **1i** groups, respectively. Individual reaction of compound **1g**, **1h** or **1i** with various arylhydrazines **2a**, **2b**, **2d** and **2f**, respectively in acetonitrile and diethyl amine didn't furnish neither any C-arylated product nor any hydrazone product instead starting materials were recovered as such even after 48 hours (Scheme 4a). Similar fact was also observed (Scheme 4b) when various arylhydrazines **2a**, **2b**, **2d**, **2f** and **2i** failed to react with the protected kojic acid derivatives **4a**, **4b** and **4c**. This signifies that the attack of aryl radical is not feasible if the hydroxyl group is protected and thus underlying the necessity of free hydroxyl group for the reaction to take place. Next we turned our attention on kojic acid **4** as it has another functionalisable site (next to hydroxymethyl group) for C-arylation. We treated compound **4** with excess of phenyl hydrazine **2i** assuming that the bi-arylated product should form however, only mono C-arylated product **5i** was obtained with no traces of formation of bi-arylated product (Scheme 4c). Hence, the role of free hydroxyl group on the C-arylation reaction was evident. Further, the role of hydroxymethyl group present in **4** on the product formation, if any was studied. The hydroxymethyl group was protected as OBn by reported literature procedure.[16] Treatment of compound **4d** with **2a** in acetonitrile and diethyl amine furnished mono C-arylated product **6** in 74% yield (Scheme 4d). This proves that hydroxymethyl group has no role on the course of reaction.

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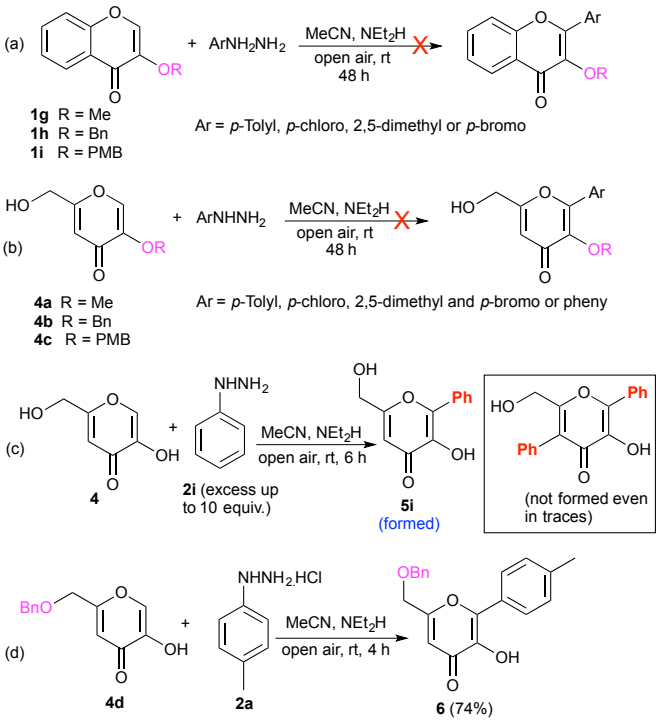
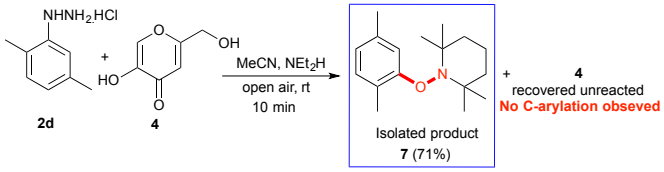


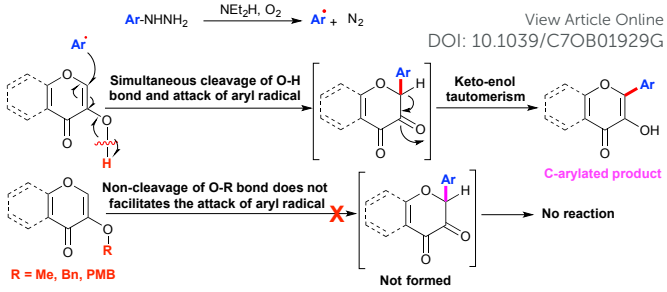
Scheme 4 Studies towards the role of free hydroxyl and hydroxymethyl group in C-arylation.

In order to prove C-arylation of 3-hydroxychromone and pyran-4-one taking place *via* free radical reaction, we carried out an ideal reaction of 2,5-dimethyl phenylhydrazine hydrochloride **2d** with kojic acid **4** in presence of radical scavenger TEMPO under our optimised reaction condition, which furnished the sole product **7** without any trace of C-arylated product. It proves that C-arylation of 3-hydroxychromone and pyran-4-one takes place *via* free radical mechanism (Scheme 5).



Scheme 5 Radical trapping experiment with TEMPO.

Based on the above observations, a plausible mechanism of C-arylation of 3-hydroxychromone and pyran-4-one moieties has been delineated in Scheme 6. Presumably, at first the aryl hydrazine forms aryl radical in presence of base and atmospheric oxygen with the elimination of N_2.[17] The breaking of O-H bond facilitates the attack of aryl radical on C-2 position. The proton at C-2 further then undergoes a keto-enol tautomerism to furnish the desired C-arylated product. This concludes that the possible keto-enol tautomerism in 3-hydroxychromones and pyran-4-ones is the real driving force for the position specific C-arylations.



Scheme 6 Plausible mechanism of C-arylation on 3-hydroxychromone and 5-hydroxy pyran-4-one.

Conclusions

In summary, we have developed a mild and efficient transition-metal free method for C-arylation of 3-hydroxychromone and 5-hydroxy pyran-4-one using arylhydrazines as arylating source and air as an oxidant under basic reaction conditions. The unequivocal role of hydroxyl group in the formation of C-arylated product has been delineated. We also feel that present protocol will be useful for several such types of desired C-arylations essential for total synthesis of natural and unnatural products.

Experimental section

General Information. All melting points were recorded on a Büchi melting point apparatus in open capillaries and are uncorrected. Flash chromatography was performed with CombiFlash *Rf* 200*i* equipped with UV/VIS and ELSD (Isco Teledyne Inc., USA) using RediSep® pre-packed column (SiO_2). ^1H NMR spectra were recorded on a Bruker 200, 400 or 500 MHz spectrometer and ^{13}C NMR spectra were recorded at 50, 100 or 125 MHz, respectively. Chemical shifts are reported as δ values (ppm) relative to residual solvent peak of Methanol-D_4 or $CDCl_3$. HRMS (ESI) was recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. Petroleum ether and ethyl acetate were distilled by usual methods. All the starting materials and dried solvent such as DMF and DCM were purchased and used without further drying.

Synthesis of 3aa and 3ba.

In 10 ml round bottom flask, compound **1a/1b** (0.25 mmol, 1 equiv.) was dissolved in DMSO (3 mL) at rt. Then *p*-tolyl hydrazine hydrochloride **2a** (48 mg, 0.30 mmol, 1.2 equiv.) was added to the round bottom flask followed by addition of potassium carbonate (104 mg, 0.75 mmol, 3.0 equiv.). The reaction was stirred in open air and monitored by TLC. After complete consumption of **1a/1b**, the reaction mixture was diluted with water (20 mL), extracted with ethyl acetate (3×15 mL) and washed with brine (2×10 mL). The organic layer was dried over anhydrous $Na_2SO_4$and the solvent was concentrated under reduced pressure to furnish a residue, which was purified by flash chromatography (RediSep SiO_2 column, 12 g) using pet ether-ethyl acetate as eluent (9:1 to 4:1) to furnish **3aa/3ba** respectively.

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(4*H*-Chromen-4-ylidene)-2-(*p*-tolyl)hydrazine (3aa): Yellow solid (46 mg, 72%); m.p. 133–137 ˚C; R_f = 0.35 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.06 (s, 1H), 8.21–8.19 (m, 2H), 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56–7.48 (m, 1H), 7.39–7.36 (m, 4 H), 7.09–7.05 (m, 1H), 7.01–6.92 (m, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 192.2, 162.7, 142.2, 138.0, 136.0, 131.2, 130.4, 130.2, 119.8, 119.1, 118.6, 21.1; LCMS (ESI): *m/z* 250.1for $C_{16}H_{14}N_2O_2$ $(M)^+$

3-((2-(*p*-tolyl)hydrazono)methyl)-4*H*-chromen-4-one (3ba): Yellow solid (38 mg, 55%); m.p. 117–119 ˚C; R_f = 0.38 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.04 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.64–7.60 (m, 2H), 7.56–7.48 (m, 1H), 7.32–7.28 (m, 2H), 7.07 (dd, *J* = 8.5, 0.9 Hz 1H), 7.01–6.93 (m, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 192.2, 162.7, 142.2, 138.0, 136.9, 136.0, 131.2, 130.4, 130.2, 123.2, 120.1, 119.7, 119.1, 118.6, 21.1; HRMS: *m/z* for $C_{17}H_{15}O_2N_2$ $(M+H)^+$: calcd 279.1128, found 279.1121.

General Procedure for the Synthesis of 3da–3fi.

In a 10-ml round bottom flask, compound **1d–f** (0.25 mmol, 1 equivalent) was dissolved in acetonitrile (3 mL) at rt. Then aryl hydrazine hydrochloride **2a–i** (0.375 mmol, 1.5 equiv.) was added to the round bottom flask followed by addition of diethyl amine (90 µL, 0.875 mmol, 3.5 equiv.). The reaction was stirred in open air and monitored by TLC. After complete consumption of starting material, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (RediSep, SiO_2 column, 12 g) using ethyl acetate-pet ether as eluent (0→1:49) to furnish corresponding **3da–3fi**.

3-Hydroxy-2-(*p*-tolyl)-4*H*-chromen-4-one (3da): Yellow solid (48 mg, 78%); m.p. 190–192 ˚C; R_f = 0.44 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, *J* = 8.0 Hz, 1H), 8.16–8.14 (m, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.34–7.33 (m, 2H), 7.05 (brs, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 155.4, 145.4, 140.6, 138.2, 133.5, 129.4, 128.3, 127.7, 125.4, 124.5, 120.7, 118.3, 21.6; HRMS: *m/z* for $C_{16}H_{13}O_3$ $(M+H)^+$: calcd 253.0859, found 253.0857, *m/z* for $C_{16}H_{12}O_3Na$ $(M+Na)^+$: 275.0679, found 275.0674.

2-(4-Chlorophenyl)-3-hydroxy-4*H*-chromen-4-on (3db): Yellow solid (49 mg, 73%); m.p.197–199 ˚C; R_f = 0.42 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25–8.20 (m, 3H), 7.73–7.69 (m, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.50–7.48 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 155.4, 143.9, 138.6, 136.3, 134.0, 129.6, 129.1, 129.0, 125.6, 124.8, 120.7, 118.4; HRMS: *m/z* for $C_{15}H_{10}O_3Cl$ $(M+H)^+$: calcd 273.0313, found 273.0312, *m/z* for $C_{15}H_9O_3ClNa$ $(M+Na)^+$: 295.0132, found 295.0129.

3-Hydroxy-2-(*o*-tolyl)-4*H*-chromen-4-one (3dc): Yellow solid (50 mg, 80%); m.p. 189–191 ˚C; R_f = 0.44 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.72–7.69 (m, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45–7.41 (m, 2H), 7.37–7.33 (m, 2H), 6.53 (brs, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 155.9, 147.8, 138.4, 137.7, 133.6, 130.9, 130.4, 130.0, 129.8, 125.8, 125.6, 124.6, 121.2, 118.4, 20.1; HRMS: *m/z* for $C_{16}H_{13}O_3$ $(M+H)^+$: calcd 253.0859, found 253.0862.

2-(2,5-Dimethylphenyl)-3-hydroxy-4*H*-chromen-4-one (3dd): Yellow solid (52 mg, 79%); m.p. 205–207 ˚C; R_f = 0.48 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.53–7.51 (m, 1H), 7.46–7.41 (m, 2H), 7.25–7.23 (m, 2H), 6.54 (brs, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 156.0, 148.1, 138.4, 135.4, 134.6, 133.6, 131.4, 130.9, 130.2, 129.8, 125.6, 124.7, 121.3, 118.5, 21.0, 19.7; HRMS: *m/z* for $C_{17}H_{15}O_3$ $(M+H)^+$: calcd 267.1016, found 267.1017.

2-(2,4-Dimethylphenyl)-3-hydroxy-4*H*-chromen-4-one (3de): Yellow solid (53 mg, 81%); m.p. 199–201 ˚C; R_f = 0.48 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.71–7.67 (m, 1H), 7.52–7.49 (m, 2H), 7.44–7.41 (m, 1H), 7.18–7.15 (m, 2H), 6.52 (brs, 1H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 155.9, 148.1, 140.8, 138.4, 137.6, 133.6, 131.7, 129.8, 127.2, 126.6, 125.6, 124.6, 121.3, 118.5, 21.5, 20.1; HRMS: *m/z* for $C_{17}H_{15}O_3$ $(M+H)^+$: calcd 267.1016, found 267.1014, *m/z* for $C_{17}H_{14}O_3Na$ $(M+Na)^+$: calcd 289.0835, found 289.0834.

2-(4-Bromophenyl)-3-hydroxy-4*H*-chromen-4-one (3df): Yellow solid (54 mg, 70%); m.p. 242–244 ˚C (decomposition); R_f = 0.42 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27–8.24 (m, 1H), 8.16–8.14 (m, 2H), 7.75–7.70 (m, 1H), 7.69–7.66 (m, 2H), 7.62–7.59 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 155.4, 143.9, 138.6, 133.9, 131.9, 130.0, 129.2, 125.5, 124.7, 120.6, 118.3; HRMS: *m/z* for $C_{15}H_{10}O_3Br$ $(M+H)^+$: calcd 316.9808, found 316.9808.

2-(4-Fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (3dg): Yellow solid (48 mg, 76%); m.p. 163–165 ˚C; R_f = 0.43 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.32–8.17 (m, 3H), 7.76–7.68 (m, 1H), 7.61–7.56 (m, 1H), 7.47–7.42 (m, 1H), 7.27–7.18 (m, 2H), 7.07 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.4, 166.1, 161.1, 155.4, 144.1, 138.2, 133.8, 130.1, 129.9, 127.3, 125.5, 124.6, 118.2, 116.0, 115.6; HRMS: *m/z* for $C_{15}H_{10}FO_3$ $(M+H)^+$: calcd 257.0608, found 257.0603.

2-(4-Chlorophenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (3eb): Yellow solid (45 mg, 64%); m.p. 210 ˚C (decomposition); R_f = 0.40 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23–8.21 (m, 2H), 8.03 (s, 1H), 7.55–7.48 (m, 4H), 7.04 (brs, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 153.8, 138.5, 136.1, 135.3, 134.7, 129.7, 129.0, 128.9, 124.6, 120.3, 118.0, 20.9; HRMS: *m/z* for $C_{16}H_{12}O_3Cl$ $(M+H)^+$: calcd 287.0469, found 287.0473.

3-Hydroxy-6-methyl-2-(*o*-tolyl)-4*H*-chromen-4-one (3ec): Yellow solid (54 mg, 82%); m.p. 187–188 ˚C; R_f = 0.44 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (brs, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.52–7.50 (m, 1H), 7.44–7.40 (m, 2H), 7.38–7.32 (m, 2H), 6.47 (brs, 1H), 2.49 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.2, 154.3, 147.6, 138.3, 137.7, 135.0, 134.6, 130.8, 130.4, 130.1, 129.8, 125.7, 124.6, 120.9, 118.2, 21.0, 20.1; HRMS: *m/z* for $C_{17}H_{15}O_3$ $(M+H)^+$: calcd 267.1016, found 267.1017.

2-(2,4-Dimethylphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (3ee): Yellow solid (52 mg, 74%); m.p. 250 ˚C (decomposition); R_f = 0.47 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.51–7.49 (m, 2H), 7.42–7.40 (m, 1H), 7.18–7.15 (m, 3H), 6.45 (brs, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 154.2, 147.9, 140.6, 138.2, 137.5, 135.0, 134.5, 131.6, 129.7, 127.2, 126.5, 124.6, 120.9, 118.2, 21.4, 21.0, 20.0; HRMS: *m/z* for $C_{18}H_{17}O_3$ $(M+H)^+$: calcd 281.1172, found 281.1175.

3-Hydroxy-2-(4-methoxyphenyl)-6-methyl-4*H*-chromen-4-one (3eh): Yellow solid (58 mg, 82%); m.p. 256–258 ˚C; R_f = 0.43 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25–8.23 (m, 2H), 8.02 (brs, 1H), 7.51–7.46 (m, 2H), 7.06–7.04 (m, 2H), 7.00 (brs, 1H), 3.90 (s, 3H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 161.0, 153.6, 145.2, 137.6, 134.8, 134.3, 129.5, 124.5, 123.7, 120.4, 117.9,

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114.1, 55.4, 20.9; HRMS: *m/z* for $C_{17}H_{15}O_4$ $(M+H)^+$: calcd 283.0965, found 283.0966.

3-Hydroxy-6-methoxy-2-(*p*-tolyl)-4*H*-chromen-4-one (3fa): Yellow solid (62 mg, 88%); m.p. 189–191 ˚C; R_f = 0.42 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15–8.14 (m, 2H), 7.56 (brs, 1H), 7.52–7.51 (m, 1H), 7.38–7.28 (m, 3H), 6.98 (brs, 1H), 3.92 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 156.5, 150.5, 145.2, 140.5, 137.8, 129.4, 128.4, 127.7, 124.3, 121.1, 119.7, 103.8, 56.0, 21.6; HRMS: *m/z* for $C_{17}H_{15}O_4$ $(M+H)^+$: calcd 283.0965, found 283.0964.

2-(2,5-Dimethylphenyl)-3-hydroxy-6-methoxy-4*H*-chromen-4-one (3fd): Yellow solid (56 mg, 76%); m.p. 242–244 ˚C; R_f = 0.42 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (brs, 1H), 7.46–7.40 (m, 2H), 7.31–7.29 (m, 1H), 7.27–7.19 (m, 2H), 6.49 (brs, 1H), 3.93 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 156.5, 151.0, 147.9, 138.0, 135.3, 134.5, 131.2, 130.7, 130.1, 129.8, 124.3, 121.7, 119.8, 103.9, 7.0, 56.0, 20.9, 19.5; HRMS: *m/z* for $C_{18}H_{17}O_4$ $(M+H)^+$: calcd 297.1121, found 297.1124.

3-Hydroxy-6-methoxy-2-phenyl-4*H*-chromen-4-one (3fi): Yellow solid (48 mg, 72%)[a]; m.p. 185–187 ˚C; R_f = 0.40 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.28–8.23 (m, 2H), 7.57–7.47 (m, 5H), 7.35–7.28 (m, 1H), 7.04 (brs, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.1, 156.5, 150.6, 138.2, 131.2, 130.1, 128.6, 127.7, 124.5, 121.1, 119.8, 103.8, 56.0; HRMS: *m/z* for $C_{16}H_{13}O_4$ $(M+H)^+$: calcd 269.0808, found 269.0801.

[a]base used (65 µL, 0.625 mmol, 2.5 equiv.)

General Procedure for the Synthesis of 5a–5k.

In a 10 mL round bottom flask, kojic acid **4** (35 mg, 0.25 mmol, 1 equiv.) was dissolved in acetonitrile (3 mL) at rt. Then aryl hydrazine hydrochloride **2a–k** (0.375 mmol, 1.5 equiv.) was added to the round bottom flask followed by addition of diethyl amine (90 µL, 0.875 mmol, 3.5 equiv.). The reaction was stirred in open air and monitored by TLC. After complete consumption of kojic acid **4**, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (RediSep, SiO_2 column, 12 g) using pet ether-ethyl acetate as eluent (0→1:1, gradient) to furnish the desired product.

3-Hydroxy-6-(hydroxymethyl)-2-(*p*-tolyl)-4*H*-pyran-4-one (5a): Pale yellow solid (43 mg, 75%); m.p. 123–125 ˚C; R_f = 0.32 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 200 MHz): δ 8.01–7.96 (m, 2H), 7.30–7.26 (m, 2H), 6.52 (s, 1H), 4.52 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (CD_3OD, 50 MHz): δ 176.8, 169.4, 147.5, 143.3, 141.3, 130.2, 129.4, 128.3, 109.0, 61.4, 21.5; HRMS: *m/z* for $C_{13}H_{13}O_4$ $(M+H)^+$: calcd 233.0808, found 233.0805; *m/z* for $C_{13}H_{12}O_4Na$ $(M+Na)^+$: calcd 255.0628, found 255.0623

2-(4-Chlorophenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5b): Yellow solid (43 mg, 68%); m.p. 171–173 ˚C; R_f = 0.25 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 8.17–8.12 (m, 2H), 7.55–7.50 (m, 2H), 6.56 (s, 1H), 4.56 (s, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 175.3, 168.2, 144.5, 142.5, 135.1, 129.5, 128.3, 107.7, 60.0; HRMS: *m/z* for $C_{12}H_{10}O_4Cl$ $(M+H)^+$: calcd 253.0262, found 253.0258.

3-Hydroxy-6-(hydroxymethyl)-2-(*o*-tolyl)-4*H*-pyran-4-one (5c): White solid (45 mg, 76%); m.p. 128–130˚C; R_f = 0.35 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.46–7.45 (m, 1H), 7.39–7.36 (m, 1H), 7.33–7.31 (m, 1H), 7.29–7.26 (m, 1H), 6.57 (s, 1H), 4.46 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 177.0, 170.0, 150.3, 143.8, 138.9, 131.6, 131.3, 126.8, 109.9, 61.5, 20.1; HRMS: *m/z* for $C_{13}H_{13}O_4$ $(M+H)^+$: calcd 233.0808, found 233.0806; *m/z* for $C_{13}H_{12}O_4Na$ $(M+Na)^+$: calcd 255.0628, found 255.0624.

2-(2,5-Dimethylphenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5d): Brown solid (49 mg, 78%); m.p. 130–132˚C; R_f = 0.42 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 500 MHz): δ7.27 (s, 1H), 7.19 (s, 2H), 6.56 (s, 1H), 4.46 (s, 2H), 2.34 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 177.0, 170.0, 155.5, 143.7, 136.5, 135.8, 132.0, 131.6, 131.4, 109.9, 61.6, 21.0, 19.7; HRMS: *m/z* for $C_{14}H_{15}O_4$ $(M+H)^+$: calcd 247.0965, found 247.0961; *m/z* for $C_{14}H_{14}O_4Na$ $(M+Na)^+$: calcd 269.0784, found 269.0780.

2-(2,4-Dimethylphenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5e): Brown solid (48 mg, 77%); m.p. 132–134 ˚C; R_f = 0.40 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.39 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.57 (s, 1H), 4.47 (s, 2H), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 177.2, 170.0, 150.8, 144.0, 141.6, 138.8, 132.3, 131.0, 128.6, 127.5, 110.0, 61.6, 21.5, 20.2; HRMS: *m/z* for $C_{14}H_{15}O_4$ $(M+H)^+$: calcd 247.0965, found 247.0963; *m/z* for $C_{14}H_{14}O_4Na$ $(M+Na)^+$: calcd 269.0784, found 269.0781.

2-(4-Bromophenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5f): Pale yellow solid (49 mg, 65%); m.p. 140–142˚C; R_f = 0.28 (PE/EtOAc, 1:1);^{1}H NMR (CD_3OD, 500 MHz): δ 8.05–8.04 (m, 2H), 7.66–7.64 (m, 2H), 6.54 (s, 1H), 4.53 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 177.0, 169.8, 146.1, 144.1, 132.9, 131.5, 130.1, 125.0, 109.3, 61.5; HRMS: *m/z* for $C_{12}H_{10}O_4Br$ $(M+H)^+$: calcd 296.9757, found 296.9752.

2-(4-Fluorophenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5g): Yellow solid (44 mg, 74%); m.p. 129–131 ˚C; R_f = 0.38 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 200 MHz): δ 8.24–8.17 (m, 2H), 7.31–7.22 (m, 2H), 6.58 (s, 1H), 4.57 (s, 2H); ^{13}C NMR (CD_3OD, 50 MHz): δ 176.8, 169.5, 130.8, 130.6, 116.7, 116.3, 109.1, 61.4; HRMS: *m/z* for $C_{12}H_{10}O_4F$ $(M+H)^+$: calcd 237.0558, found 237.0557.

3-Hydroxy-6-(hydroxymethyl)-2-(4-methoxyphenyl)-4*H*-pyran-4-one (5h): Yellow solid (46 mg, 73%); m.p. 135–136 ˚C; R_f = 0.38 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 200 MHz): δ 8.11–8.06 (m, 2H), 7.05–7.01 (m, 2H), 6.52 (s, 1H), 4.53 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (CD_3OD, 50 MHz): δ 169.2, 162.5, 147.9, 142.8, 130.2, 115.1, 109.1, 61.6, 56.0; HRMS: *m/z* for $C_{13}H_{13}O_5$ $(M+H)^+$: calcd 249.0757, found 249.0759.

3-Hydroxy-6-(hydroxymethyl)-2-phenyl-4*H*-pyran-4-one (5i): Brown solid (39 mg, 72%);[a] m.p. 124–126 ˚C; R_f = 0.30 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 400 MHz): δ 8.12–8.10 (m, 2H), 7.50–7.42 (m, 3H), 6.54 (s, 1H), 4.54 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.4, 168.2, 145.7, 142.2, 130.8, 129.4, 128.1, 107.6, 60.0; HRMS: *m/z* for $C_{12}H_{11}O_4$ $(M+H)^+$: calcd 219.0652, found 219.0651.

[a]base used (65 µL, 0.625 mmol, 2.5 equiv.)

3-Hydroxy-6-(hydroxymethyl)-2-(2,4,6-trichlorophenyl)-4*H*-pyran-4-one (5j): White solid (36 mg, 44%); m.p. 128–130 ˚C; R_f = 0.35 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.66 (s, 2H), 6.61 (s, 1H), 4.47 (s, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 176.9, 170.8, 144.1, 138.7, 138.1, 129.6, 110.5, 61.4; HRMS: *m/z* for $C_{12}H_8O_4Cl_3$ $(M+H)^+$: calcd 320.9483, found 320.9486.

2-(2,4-Dichlorophenyl)-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (5k): Yellow solid (44 mg, 62%); m.p. 135–137 ˚C; R_f = 0.35 (PE/EtOAc, 1:1); ^{1}H NMR (CD_3OD, 200 MHz): δ 7.65–7.62 (m, 1H), 7.58 (s, 1H), 7.49–7.44 (m, 1H), 6.56 (s, 1H), 4.46 (s, 2H); ^{13}C NMR (CD_3OD, 50 MHz): δ 177.0, 170.4, 138.0, 136.0, 134.2, 131.0, 128.5,

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110.1, 61.4; HRMS: *m/z* for $C_{12}H_9O_4Cl_2$ $(M+H)^+$: calcd 286.9872, found 286.9876.

General Procedure for the Synthesis of 6.

In a 10 mL round bottom flask, 6-*O*-benzylated kojic acid **4d** (58 mg, 0.25 mmol, 1 equiv.) was dissolved in acetonitrile (3 mL) at rt. Then *p*-tolyl hydrazine hydrochloride **2a** (59 mg, 0.375 mmol, 1.5 equiv.) was added to the round bottom flask followed by addition of diethyl amine (90 µL, 0.875 mmol, 3.5 equiv.). The reaction was stirred in open air and monitored by TLC. After complete consumption of **4d**, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (RediSep, SiO_2 column, 12 g) using pet ether-ethyl acetate as eluent (4:1, isocratic).

6-((Benzyloxy)methyl)-3-hydroxy-2-(*p*-tolyl)-4*H*-pyran-4-one (6): Yellow solid (59 mg, 74%); m.p. 133–135 ˚C; R_f = 0.40 (PE/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.97–7.93 (m, 2H), 7.42–7.28 (m, 7H), 6.60 (s, 1H), 4.66 (s, 2H), 4.46 (s, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.3, 164.2, 145.2, 141.5, 140.2, 136.9, 129.4, 128.7, 128.3, 127.9, 127.7, 126.9, 109.1, 73.2, 67.9, 21.5; HRMS: *m/z* for $C_{20}H_{19}O_4$ $(M+H)^+$: calcd 323.1278, found 323.1275, *m/z* for $C_{20}H_{18}O_4Na$ $(M+Na)^+$: calcd 345.1097, found 345.1091.

Radical Trapping Experiment: General Procedure for the Synthesis of 7.

In a 10 mL round bottom flask, kojic acid **4** (71 mg, 0.50 mmol, 1 equiv.), 2,5 dimethyl phenyl hydrazine hydrochloride **2d** (86 mg, 0.50 mmol, 1 equiv.), TEMPO (92 mg, 0.60 mmol, 1.2 equiv), was dissolved in acetonitrile (3 mL) at rt. Then diethyl amine (180 µL, 1.75 mmol, 3.5 equiv.) was added in the reaction medium. The reaction mixture was stirred in open air and monitored by TLC. After complete consumption of **2d**, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography using pet ether-ethyl acetate as eluent (50:1, isocratic).

1-(2,5-Dimethylphenoxy)-2,2,6,6-tetramethylpiperidine (7): Colourless oil (92 mg, 71%); R_f = 0.85 (PE/EtOAc, 9:1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29 (s, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 6.7 Hz, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 1.67–1.40 (m, 6H), 1.25 (s, 6H), 0.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.9, 135.8, 129.7, 120.0, 119.6, 114.5, 60.3, 39.7, 32.7, 21.6, 20.8, 17.2, 15.9; HRMS: *m/z* for $C_{17}H_{28}ON$ $(M+H)^+$: calcd 262.2165, found 262.2167.

Conflicts of interest

There are no conflicts to declare.

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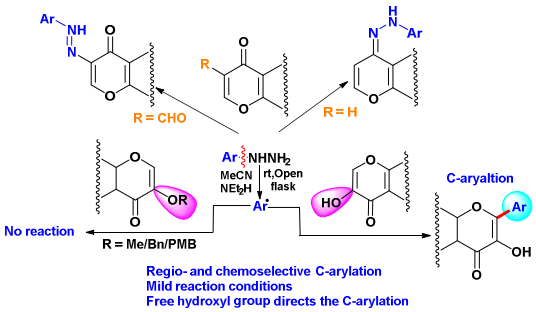
Graphical Abstract

Hydroxyl directed C-arylation: synthesis of 3-hydroxyflavones and 2-phenyl-3-hydroxy pyran-4-ones under transition-metal free conditions

Sayantan Paul and Asish K. Bhattacharya

Hydroxyl assisted, efficient, transition-metal free and direct C-arylation of 3-hydroxychromone and 5-hydroxy pyran-4-one moieties in presence of base, air as oxidant and arylhydrazines as arylating agent to furnish highly biologically active 3-hydroxyflavones and 2-phenyl-3-hydroxy pyran-4-ones has been developed.



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