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Copper-mediated synthesis of coumestans *via* $C(sp^2)$-H functionalization: Protective group free route to coumestrol and 4′-*O*-methylcoumestrol

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ABSTRACT

A simple and efficient two step synthesis of coumestans is described. The key reaction in the synthesis is the use of easily available $Cu(OAc)_2$ for C–H functionalization of 3-(2-hydroxyphenyl)coumarin to give coumestan ring system *via* formal oxidative cyclization. This approach provided a short protective group free route to naturally occurring coumestrol and 4′-*O*-methylcoumestrol.

1. Introduction

6*H*-Benzofuro[3,2-*c*]chromen-6-ones, commonly known as coumestans are polycyclic ring systems having a coumarin ring and a benzofuran ring fused together. This ring system is found in many naturally occurring compounds distributed widely in plants.[1] Members belonging to this class of compounds includes wedelolactone, coumestrol, psoralidin, medicagol, lucernol, 4′-*O*-methylcoumestrol, desmethylwedelolactone, etc. (Fig. 1). They exhibit numerous biological activities such as anticancer, estrogenic, phytoalexin activities, anti-venom, antibacterial, antifungal, cytotoxic, and antidepressant.[2] Some coumestans inhibit protein-tyrosine phosphatase 1B[3a] and some are used in the treatment of liver diseases.[3b] These immense biological activities of coumestans have been attracting chemists since decades as an interesting synthetic target.

Coumestans have been constructed *via* several synthetic approaches.[4,5] However many of these methods have their own limitations such as multistep syntheses, expensive reagents/catalysts usage, hazardous metal catalysts, difficulty in handling of reagents and/or its excessive requirement, troublesome reaction work up and product isolation. Hence continuous search for new method/reagent/catalyst for coumestan synthesis is pursued.

2. Results and discussion

Our retrosynthetic analysis of coumestan ring system **1** suggested a straight forward two step approach *via* oxidative cyclization of 3-(2-hydroxyphenyl)coumarin **2** (Scheme 1). The required 3-(2-hydroxyphenyl)coumarin **2** can be conveniently obtained by condensation of salicylaldehyde **3** and 2-coumaranone **4** or 2-hydroxyphenylacetic acid **5**.

For the oxidative cyclization of **2** four conditions are reported in literature (Scheme 2).[6] First $Pb(OAc)_4$ in refluxing anhydrous benzene,[6a] later DDQ in refluxing anhydrous benzene,[6b] then $PdCl_2$ in presence of sodium acetate in DMF at 150 °C[6c] and recently iodine in refluxing pyridine.[6d] These oxidative cyclization methods have some limitations including low product yields, utilization of expensive reagent and limited substrate scope. Hence there is a need to develop a method involving a suitable reagent which can overcome these limitations. To our knowledge $Cu(OAc)_2$ was not employed for coumestan synthesis *via* oxidative cyclization until

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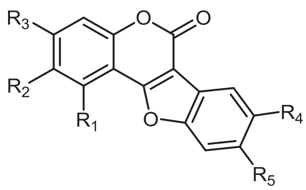
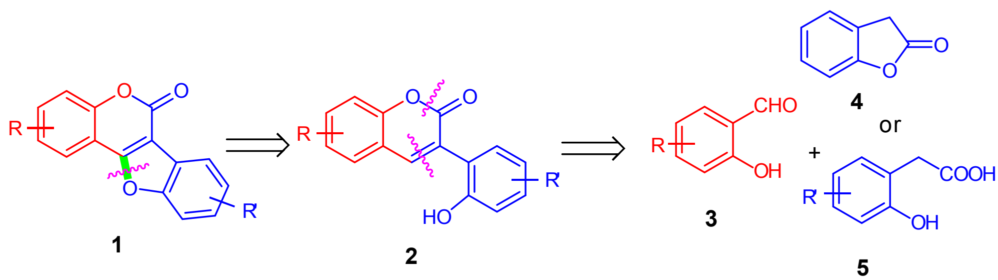
0040-4020/

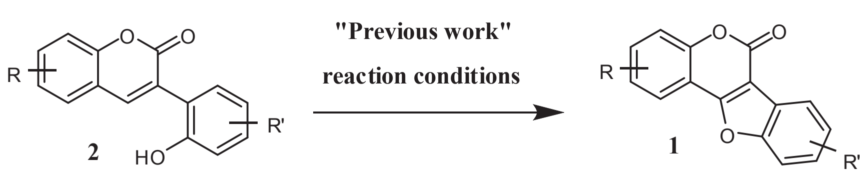


Natural coumestans	R_1	R_2	R_3	R_4	R_5
Wedelolactone	OH	H	OMe	OH	OH
Coumestrol	H	H	OH	H	OH
Psoralidin	H	prenyl	OH	H	OH
Medicagol	H	H	OH	O-CH_2-O	
Lucernol	H	OH	OH	H	OH
4'-*O*-Methylcoumestrol	H	H	OH	H	OMe
Desmethylwedelolactone	OH	H	OH	OH	OH

Fig. 1. Naturally occurring coumestans.



Scheme 1. Retrosynthetic analysis of coumestan **1**.



1. $Pb(OAc)_4$ (1.5 equiv), anhyd. benzene (30 mL), reflux, 30 min[6a]
2. DDQ (1.0 equiv), benzene, reflux, 72 h[6b]
3. $PdCl_2$ (1.0 equiv), NaOAc (13.6 equiv.), DMF, 150 °C, 24 h[6c]
4. I_2 (1.0 equiv), anhy. pyridine, reflux, 15 h[6d]

Scheme 2. Reported syntheses of coumestans **1** from **2** using various oxidizing agents.

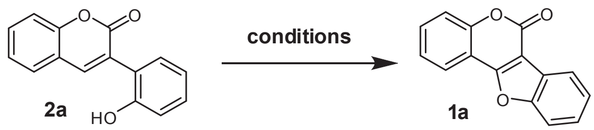
the completion of this work.

Copper salts have been widely used in organic reactions owing to its cheap availability and low toxicity. Several reviews have appeared on its role either as reagent and/or catalyst.[7] In particular $Cu(OAc)_2$ is a mild reagent/catalyst known for the synthesis of several heterocycles.[8] It has gained considerable attention for its role in the intramolecular C–O cyclization *via* C–H functionalization[8c-d] for the construction of heterocyclic compounds. For example a combination of 1.2 equiv $Cu(OAc)_2$ and 0.2 equiv of $Zn(OTf)_2$ in toluene:DMSO (20:1) has provided 11-*H*-benzofuro[3,2-*b*]chromen-11-ones and 6*H*-benzofuro[2,3-*c*]chromen-6-ones *via* insertion of oxygen into electron rich aromatic rings.[8c] Interestingly, it has not been explored for the isomeric naturally occurring 6*H*-benzofuro[3,2-*c*]chromen-6-ones (coumestans). Continuing our interest in copper chemistry[9] we envisioned the role of $Cu(OAc)_2$ in the intramolecular C–O cyclization of 3-(2-hydroxyphenyl)coumarin **2** to form coumestan **1** under forcing conditions.

At the outset 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2a** was treated with anhydrous $Cu(OAc)_2$ (1.0 equiv) in toluene under refluxing condition. To our delight the desired product **1a** was formed albeit in poor yield (Table 1, entry 1). Encouraged with this finding, we examined the reported $Cu(OAc)_2$:$Zn(OTf)_2$ in toluene:DMSO (20:1) procedure used for the synthesis of 11-*H*-benzofuro[3,2-*b*]chromen-11-ones.[8c] However, the yield did not increase. The reported C–H activation were achieved on aryl systems which were electron rich systems while in the present case we had to activate an electron deficient double bond. Hence we envisaged that higher temperature of the reaction may give us the desired product. Hence, solvents having higher boiling points (entries 3–9) were examined. Among these solvents, diphenyl ether proved to be the ideal solvent as the product yield increased substantially to 76% (entry 9). With this result, we further screened different metal reagents (entries 9–26). Employing $Cu(OAc)_2 \cdot H_2O$ diminished the product yield. Alternative Cu reagents such as $CuCl_2$, $CuBr_2$, CuI, Cu_2O and CuO also showed the formation of product among which Cu_2O gave highest yield of 75% (entries 10–15). The more reactive $Cu(OTf)_2$ gave 40% yield on refluxing in *p*-xylene (entry 16) and in diphenyl ether the yield was increased to 63% with reduced time (entry 17). Cu metal also proved effective for this cyclization (entries 18–19).

Due to the shorter reaction time and the easy availability, anhydrous $Cu(OAc)_2$ was chosen for further studies with respect to its concentration and temperature (Table 2). It must be noted that the absence of $Cu(OAc)_2$ showed no product formation (entry 1). Catalytic amount of $Cu(OAc)_2$ was effective in producing 66 and 70% yields with longer reaction time (entries 2–3) and 1.0 equiv proved to be optimum $Cu(OAc)_2$ concentration giving maximum yield at a

Table 1
Optimization of the reaction conditions for the synthesis of coumestans.[a]



Entry	Reagent	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2$	Toluene	110	24	7
2[c]	$Cu(OAc)_2$:$Zn(OTf)_2$	Toluene:DMSO (20:1)	120	24	7
3	$Cu(OAc)_2$	*p*-Xylene	138	24	20
4	$Cu(OAc)_2$	Acetic acid	118	24	0
5	$Cu(OAc)_2$	DMF	153	24	15
6	$Cu(OAc)_2$	DMA	165	24	6
7	$Cu(OAc)_2$	*o*-DCB	180	24	30
8	$Cu(OAc)_2$	DMSO	189	24	ND
9	**$Cu(OAc)_2$**	**Diphenyl ether**	**258**	**6**	**76**
10	$Cu(OAc)_2 \cdot H_2O$	Diphenyl ether	258	5	55
11	$CuCl_2$	Diphenyl ether	258	24	69
12	$CuBr_2$	Diphenyl ether	258	24	48
13	CuI	Diphenyl ether	258	24	19
14	Cu_2O	Diphenyl ether	258	24	75
15	CuO	Diphenyl ether	258	16	60
16	$Cu(OTf)_2$	*p*-xylene	138	24	40
17	$Cu(OTf)_2$	Diphenyl ether	258	16	63
18	Cu (nanopowder)	Diphenyl ether	258	24	74
19	Cu (metal powder)	Diphenyl ether	258	24	72
20	$Pd(OAc)_2$	Diphenyl ether	258	18	86
21[d]	$Pd(OAc)_2$	Diphenyl ether	258	24	RI
22[d]	$PdCl_2$	Diphenyl ether	258	24	RI
23	10 wt% of 10% Pd/C	Diphenyl ether	258	12	RI
24	20 wt% of 10% Pd/C	Diphenyl ether	258	12	RI
25	30 wt% of 10% Pd/C	Diphenyl ether	258	12	RI
26	50 wt% of 10% Pd/C	Diphenyl ether	258	12	78

ND: Not determined.
RI: Reaction incomplete.
Bold signifies the optimum condition.
[a] Conditions: **2a** (0.4 mmol), reagent (0.4 mmol) and solvent 10 mL, under open air.
[b] Isolated yields.
[c] 0.48 mmol of $Cu(OAc)_2$:0.08 mmol of $Zn(OTf)_2$ were used.
[d] 0.04 mmol of reagent was used.

Table 2
Optimization of $Cu(OAc)_2$ concentration and temperature for the synthesis of coumestan **1a** from **2a**.[a]

Entry	Temperature (°C)	$Cu(OAc)_2$ (equiv.)	Time (h)	Yield (%)[b]
1	258	0.0	6	00
2	258	0.2	24	66
3	258	0.5	12	70
4	**258**	**1.0**	**6**	**76**
5	258	1.2	11	70
6	258	2.0	14	56
7	100	1.0	24	25
8	150	1.0	24	50
9	170–180	1.0	12	62
10	200	1.0	10	64

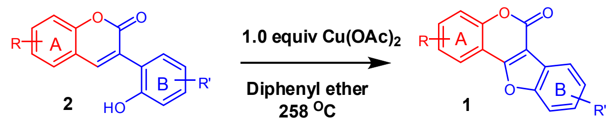
Bold signifies the optimum condition.
[a] Conditions: **2a** (0.4 mmol), $Cu(OAc)_2$ and diphenyl ether (10 mL) at above mentioned temperature under open air.
[b] Isolated yields.

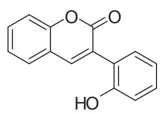
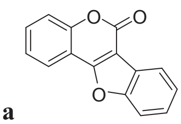
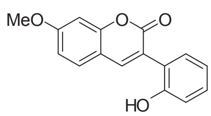
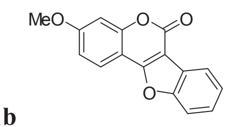
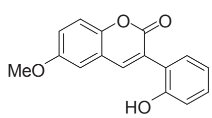
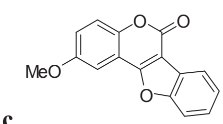
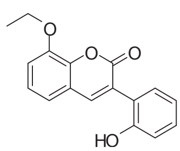
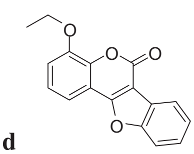
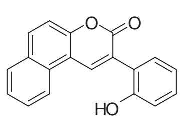
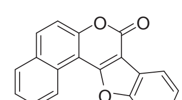
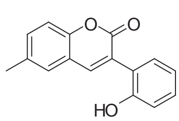
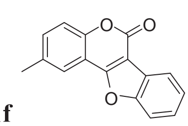
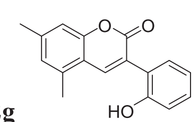
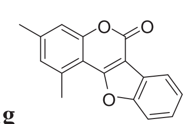
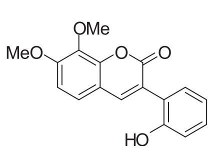
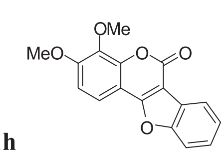
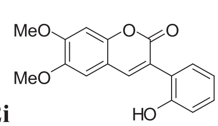
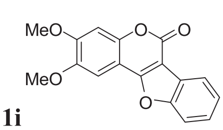
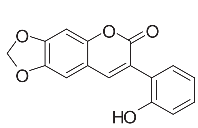
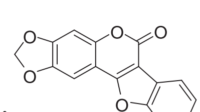
faster rate (entry 4). Furthermore on increasing its concentration resulted in decreased product yield (entries 5–6). With 1.0 equiv of $Cu(OAc)_2$ reactions were performed at different temperatures (entries 7–10) which revealed that the product yield increases with increase in temperature. Hence 258 ^{O}C was found to be the optimum temperature (entry 4).

The optimum reaction conditions were then studied for the substrate scope (Table 3). Substituents on both the phenyl rings A and B were evaluated. Study on ring A revealed that the electron releasing methoxy and ethoxy substituent's reacted smoothly to give the desired products **1b**-**1d** in good yields. Naphthol group was very reactive to provide the expected coumestan **1e** in 80% yield. Monomethyl and dimethyl substituents were also successfully converted into the desired products **1f** and **1g**. Coumestans **1h**-**1j** were formed when dimethoxy and methylenedioxy substitutions were examined on ring A. Hydroxy substituents also reacted to produce the required coumestans **1k** and **1l** without any need of protection thus exhibiting good efficiency and practicability of this method. Coumestans bearing electron withdrawing bromo and chloro groups **1m** and **1n** were synthesized in 53 and 67% yields respectively. Strong electron withdrawing nitro group was quite reactive enough to offer the desired product **1o.**

On successfully synthesising above derivatives, we went on to explore the substitution on ring B. When methoxy substituent was employed on ring B with or without substituents on ring A, reaction went on smoothly to afford diverse coumestans **1p**-**1u** in moderate to good yields. Among these the isolation of naturally occurring[10] coumestrol dimethyl ether **1q**, dimethyl ether of sativol **1t** and trimethyl ether of lucernol **1u** was quite pleasing. The synthesis of coumestrol **1y** from compound **1q** is well known.[11] The presence of methyl group on ring B also successfully delivered coumestans **1v**

Table 3
Synthesis of coumestans *via* C–H activation using $Cu(OAc)_2$.[a,b]



Sr. No.	Substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one (2)	Time (h)	Coumestan (1)	Yield[a] (%)
1	 **2a**	6	 **1a**	76
2	 **2b**	13	 **1b**	66
3	 **2c**	6	 **1c**	72
4	 **2d**	13	 **1d**	70
5	 **2e**	8	 **1e**	80
6	 **2f**	10	 **1f**	65
7	 **2g**	17	 **1g**	67
8	 **2h**	6	 **1h**	80
9	 **2i**	8	 **1i**	77
10	 **2j**	14	 **1j**	61

(*continued on next page*)

Table 3 (*continued*)

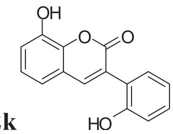
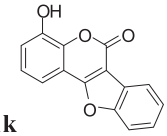
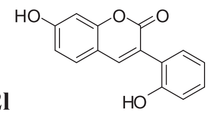
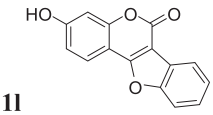
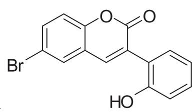
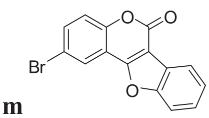
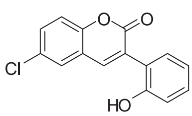
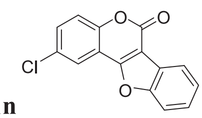
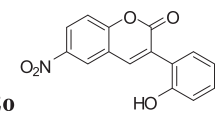
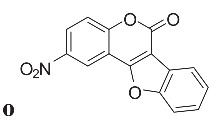
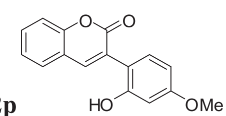
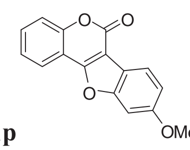
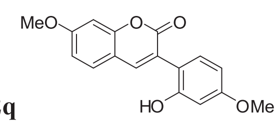
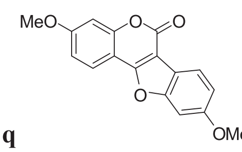
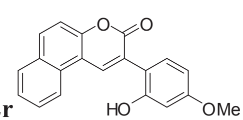
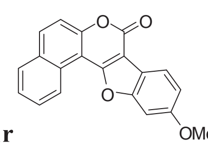
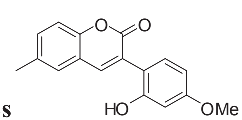
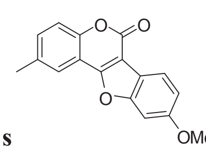
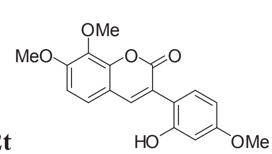
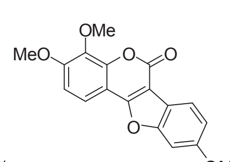
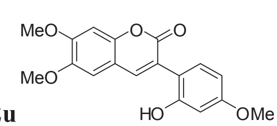
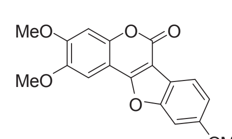
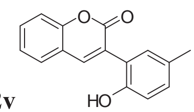
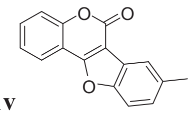
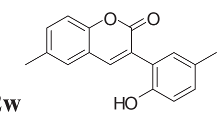
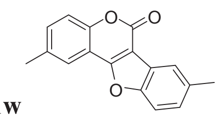
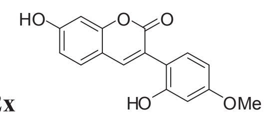
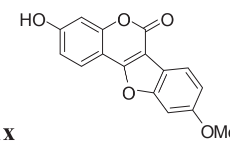
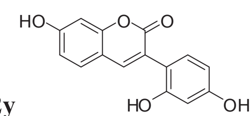
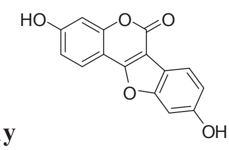
Sr. No.	Substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one (2)	Time (h)	Coumestan (1)	Yield[a] (%)
11	 **2k**	16	 **1k**	62
12	 **2l**	14	 **1l**	68
13	 **2m**	24 18[c]	 **1m**	30 53[c]
14	 **2n**	24	 **1n**	67
15	 **2o**	13	 **1o**	54
16	 **2p**	5	 **1p**	70
17	 **2q**	5	 **1q**	65
18	 **2r**	5	 **1r**	55
19	 **2s**	6	 **1s**	66
20	 **2t**	4	 **1t**	60
21	 **2u**	7	 **1u**	54

Table 3 (*continued*)

Sr. No.	Substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one (2)	Time (h)	Coumestan (1)	Yield[a] (%)
22	 **2v**	10	 **1v**	65
23	 **2w**	7	 **1w**	60
24	 **2x**	12	 **1x**	59
5	 **2y**	18	 **1y**	55

[a] Conditions: **2** (0.4 mmol), $Cu(OAc)_2$ (0.4 mmol) and diphenyl ether (10 mL), reflux under open air for 4–24 h.
[b] Isolated yields.
[c] $Cu(OAc)_2$ (0.6 mmol) was used.

and **1w** in 65 and 60% yields respectively without affecting the side chain.

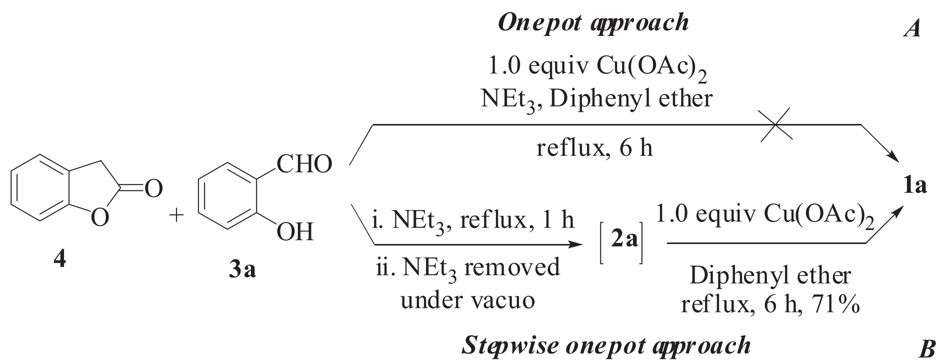
Encouraged by the formation of hydroxyl coumestans **1k** and **1l** we applied this methodology towards the protective group free synthesis of naturally occurring 4′-*O*-methylcoumestrol[1g,12] **1x** and coumestrol[1c,13] **1y**. 4′-*O*-Methylcoumestrol was isolated from *alfalfa* and various other plant species whereas coumestrol was isolated from *alfalfa*, *ladino* clover and many forage crops. The higher binding affinity of coumestrol for ERβ than other phytoestrogens makes it one of the most potent phytoestrogen.[14] Several total syntheses of coumestrol[4e,11,15] while a few of 4′-*O*-methylcoumestrol[4b,15d,16] have been reported. On subjecting the necessary starting materials to the above reaction conditions it was endearing to get both coumestans **1x** and **1y** in 59 and 55% yields respectively thus eliminating the need of protection-deprotection strategies adopted in earlier reported synthetic methods. As most of the naturally occurring coumestans contain hydroxyl and/or methoxy group/s, our methodology provides a broad scope for synthesis of such natural members of coumestan family.

The protocol was then successfully tested for the preparation of **1a** from **2a** on a larger scale (2.0 mmol) thus demonstrating its utility. Further, a one pot procedure was attempted by mixing 2-coumaranone **4**, salicylaldehyde **3a**, $Cu(OAc)_2$ and NEt_3 in diphenyl ether as the solvent system. However, no formation of **1a** was observed (Scheme 3-*A*). Hence a stepwise one pot approach was developed wherein NEt_3 was removed before addition of $Cu(OAc)_2$ giving product **1a** in good yield (Scheme 3-*B*).

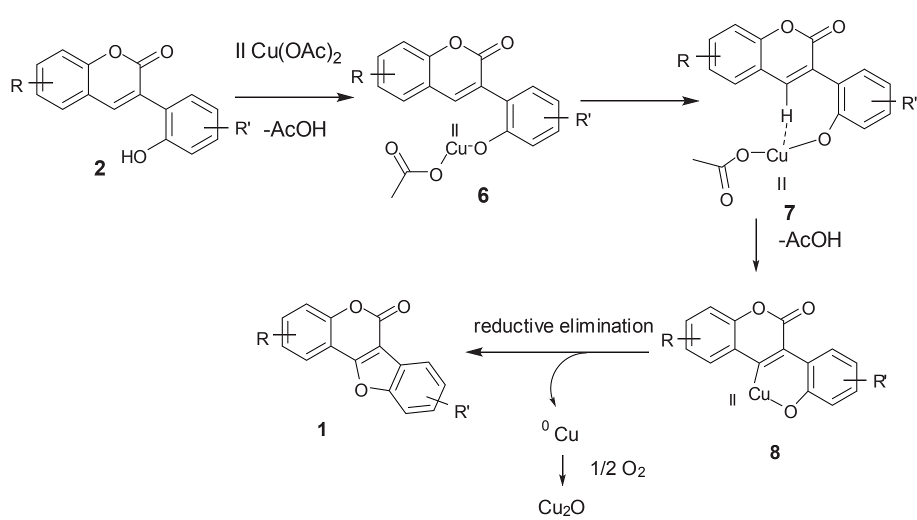
It is known that the presence of other metal impurity or “homeopathic” metal can also be responsible for such results.[17] Initially we had studied Pd metal for this oxidative cyclization. $Pd(OAc)_2$ when used in stoichiometric quantities gave coumestan in 86% yield (Table 1-entry 20). Catalytic amount of $Pd(OAc)_2$ or $PdCl_2$ resulted in incomplete reaction (entries 21–22). Similar findings were also observed for Pd/C (entries 23–26). When 50 wt% of 10% Pd/C was used 78% of coumestan was formed after 12 h (entry 26). However, due to requirement of stoichiometric amount of expensive Pd metal we had not pursued it further. Subsequently it was concluded that $Cu(OAc)_2$ was the best source for the present C–H activation. But, it was essential to confirm that presence of Pd impurity was not responsible for this $Cu(OAc)_2$ mediated cylization. Hence ICP-MS analysis of $Cu(OAc)_2$ sample was carried out. It showed the presence of 1817.97 ppb palladium in $Cu(OAc)_2$. Hence to study whether Pd has any role in this oxidative cyclization we added 0.01 equiv of $Pd(OAc)_2$ in $Cu(OAc)_2$ and repeated the experiment. However, there was not much change in the yield of the product or duration of reaction. Similar was the case when 0.1 equiv of $PdCl_2$ was added. Previously, Gong et al.[6c] had employed stoichiometric amount of $PdCl_2$ for such cyclization. Our attempt to use $PdCl_2$ under Wacker oxidation conditions [$CuCl_2$ in DMF:DMA (1:1) solvent] at 150 °C produced only trace amount of product. All these results suggest the trace amount of Pd impurity in $Cu(OAc)_2$ may not be responsible factor for this oxidative cyclization. However the role of Pd present in ppb level in contact with copper and a synergestic effect of this cannot be ruled out completely. Further study on the synergestic effects of other metal dopants/additives is a subject of future study.

To check whether the mechanism is following a radical pathway the reaction was performed in presence of a radical scavenger TEMPO. It had no effect on the yield of product **1a** suggesting an alternative mechanism. Based on this observation a speculative mechanism is proposed for this intramolecular C–O cyclization (Scheme 4). Cu(II) from $Cu(OAc)_2$ binds to electronegative hydroxyl oxygen atom of substrate **2** with the liberation of one molecule of acetic acid to form intermediate **6**. Intramolecular oxidative addition of copper to the C–H bond renders **8** *via* the elimination of another molecule of acetic acid from **7**. Finally the reductive elimination of **8** furnishes coumestan **1** and metallic copper. The formation of metallic copper was confirmed from recorded XRD (see Supporting information) of the residue left after the reaction and also from the copper mirror deposits on the walls of the reaction flask. The presence of Cu_2O seen in the XRD could be due to the aerobic oxidation of Cu at high reaction temperature.

Recently, after our studies, Zou et al.[18] have reported a synthesis of naturally occurring coumestrol and aureol *via* a combination of a



Scheme 3. Stepwise one pot synthesis of coumestan **1a**.



Scheme 4. Proposed mechanism for the formation of coumestans using $Cu(OAc)_2$.

Perkin condensation and a Cu(II)-catalyzed hydroxylation/aerobic oxidative microwave mediated coupling reaction.

3. Conclusion

In conclusion, we have developed an efficient methodology for the synthesis of coumestans. The method implements economical $Cu(OAc)_2$ as the reagent in absence of any additional reagent/additive in diphenyl ether solvent *via* C–H activation. Although the reaction temperature is high, simple reaction procedure, large substrate scope, effortless product isolation & good yields make this method attractive over reported methods. Also direct synthesis of hydroxy substituted coumestans without protection strategies makes the method noteworthy. Additional advantages are the one pot synthesis and possible use of catalytic amount of $Cu(OAc)_2$. Further scope of $Cu(OAc)_2$ as an oxidative cyclizing agent employing ligands will be undertaken in near future.

4. Experimental

4.1. General remarks

All the compounds were characterized by spectral analysis (IR; ^{1}H NMR; ^{13}C NMR) and comparison of their melting points with the literature reports. All the melting points were uncorrected. Infrared (IR) spectra were recorded in a FTIR instrument using KBr and wavenumbers given in cm^{-1}. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in DMSO-d_6/$CDCl_3$ as solvent and TMS as an internal standard. Coupling constants are reported in Hz. High resolution mass spectra (HRMS) were recorded on Q-TOF MS instrument with an electrospray source in ESI mode at IISc, Bangalore. Quantification of palladium impurity in $Cu(OAc)_2$ was detected by using ICP-MS. All the solvents were distilled prior to use. Column chromatography was performed on 60–120 mesh silica gel. All the chemical reagents and diphenyl ether were purchased from commercial sources and used without further purification unless otherwise stated. Anhydrous $Cu(OAc)_2$ was purchased from Sigma Aldrich. Substrates **2a** to **2o** were synthesized using literature procedure from 2-coumaranone **4** and substituted salicylaldehyde derivatives **3**.[19] Similarly **2p** to **2y** were synthesized from substituted salicylaldehyde derivatives **3** and 2-hydroxyphenylacetic acid derivatives **5** using literature procedure.[6c] All the reactions were carried out under atmospheric conditions without any special cautions unless otherwise stated.

4.2. General procedures

*4.2.1. General procedure for the synthesis of substrates **2a-2o**[19]*

Substituted salicylaldehyde derivative **3** (455 mg, 3.7 mmol) and 2-coumaranone **4** (500 mg, 3.7 mmol) were mixed together in a round bottom flask. To it triethylamine (15 mL) was added and refluxed for 1 h. After 1 h triethylamine was removed under vacuum and the crude solid was recrystallized from ethanol to afford pure product 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2a-2o**.

4.2.2. General procedure for the synthesis of substrates 2p-2y[6c]

Substituted salicylaldehyde derivative **3** (122 mg, 1.0 mmol), substituted 2-hydroxyphenylacetic acid **5** (182 mg, 1.0 mmol), sodium acetate (410 mg, 5.0 mmol) and acetic anhydride (245 mg, 2.4 mmol) were mixed together in a round bottom flask. To it acetic acid (4 mL) was added and refluxed for 24 h. After 24 h the solvent was removed under vacuum and water was added to it. The crude solid obtained was filtered and then loaded on column (eluent: petroleum ether/ethyl acetate) to afford pure product 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2p-2y**.

*4.2.3. General procedure for the synthesis of coumestans **1a-1y***

$Cu(OAc)_2$ (77 mg, 0.4 mmol) was added to substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2a-2y** (100 mg, 0.4 mmol) in a 25 mL round bottom flask. To it 10 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 4–24 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column (eluent: petroleum ether/ethyl acetate) to afford pure product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a-1y**.

*4.2.4. Procedure for the synthesis of coumestan **1a** on 0.5 g scale*

$Cu(OAc)_2$ (382 mg, 2.1 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2a** (500 mg, 2.1 mmol) in a 50 mL round bottom flask. To it 20 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 21 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column (eluent: petroleum ether/ethyl acetate, v/v = 10/1.5) to afford product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a** as colorless solid (296 mg, 60%).

*4.2.5. Procedure for stepwise one pot synthesis of coumestan **1a***

2-coumaranone **4** (57 mg, 0.4 mmol) and salicylaldehyde **3a** (52 mg, 0.4 mmol) were mixed together in a 25 mL round bottom flask. To it triethylamine (5 mL) was added and refluxed for 1 h. Triethylamine was removed under vacuum and to the product formed 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **2a**, $Cu(OAc)_2$ (77 mg, 0.4 mmol) and 10 mL of diphenyl ether were added. The resulting mixture was then heated to reflux for 6 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column (eluent: petroleum ether/ethyl acetate, v/v = 10/1.5) to afford product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a** as colorless solid (70 mg, 71%).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.07.057.

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