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Iron(III) catalyzed direct C-H functionalization at the C-3 position of chromone for the synthesis of fused chromeno-quinoline scaffolds

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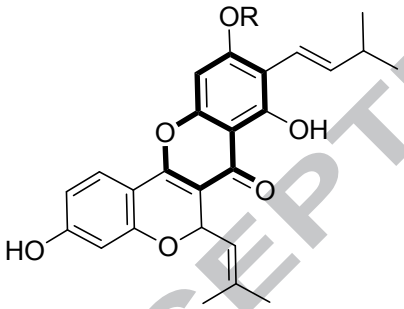
Abstract: This communication describes an iron-catalyzed route for the synthesis of 6-substituted chromeno[3,2-*c*]quinolin-7-one. The method developed does not require any pre-functionalization to execute the pivotal coupling reaction at the C-3 position of flavones. The final step involves the consecutive application of imine formation, C_{sp}^2-C_{sp}^2 coupling and oxidation reaction, with aromatic aldehydes and 2-(2-aminophenyl)-4*H*-chromen-4-one as the reactants. Presence of electron donating/withdrawing groups was well tolerated in the aldehydes and the method developed could also be extended to other substituted 2-(2-aminophenyl)-4*H*-chromen-4-one's. This is the first report of synthesis of 6-substituted chromeno[3,2-*c*]quinolin-7-one's *via* direct functionalization of the C-3 site of flavones.

Keywords: Chromones; chromeno-quinolines; $FeCl_3$; cyclization

Introduction

Chromones and their C-2 phenyl substituted analogues (flavones) are important organic molecules bestowed with diverse medicinally beneficial attributes. Some of the important pharmacological properties displayed by these compounds include antimicrobial, antitumor and anti-inflammatory activity.[1] Currently a lot of attention is also garnered by chromone-fused heterocycles, available from natural as well as synthetic sources.[2] Well known examples of this class include brosimone I and cycloartocarpin, known for their tyrosinase inhibitory activity **(Figure-1)**.[3]

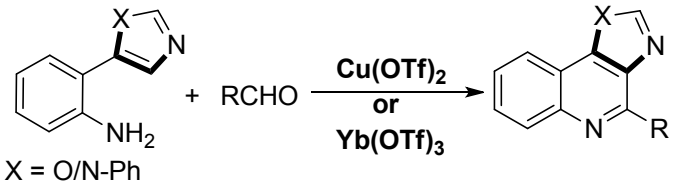


R=H(Brosimone I)
R=CH_3(Cycloartocarpin)

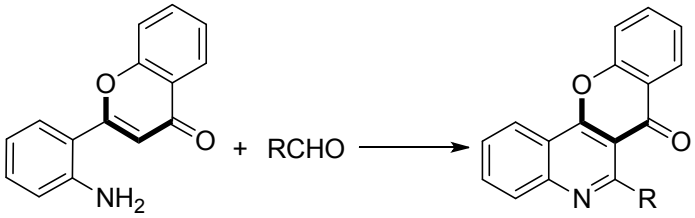
Figure 1: Chemical structures of brosimone I and cycloartocarpin.

In continuation with our efforts on synthetic and biological studies of fused-heterocycles, synthesis of chromeno fused quinoline was conceived. To the best of our knowledge, there are no reports on these molecules in the literature. Based on our prior experience with oxazolo[4,5-*c*]quinolines/imidazo[4,5-*c*]quinolines synthesis,[4] and their apparent similarity with chromones, it was felt that the most straightforward route to the target molecules would involve cyclization at the unreactive C-3 position of chromone. Thus we envisaged the application of a Pictet-Spengler inspired approach would be most appropriate to access the diverse chromeno[3,2-*c*]quinolin-7-one's **(Scheme-1)**.

Our previuos work:



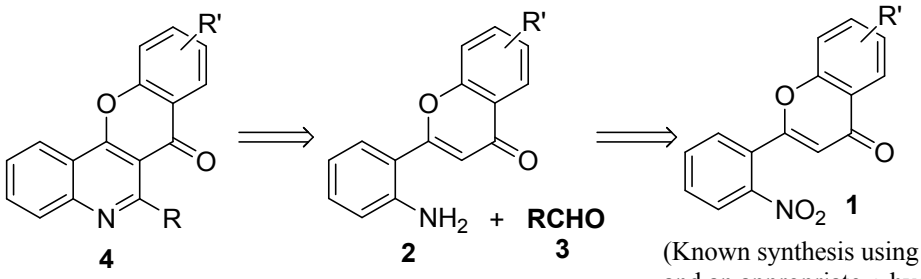
Current attempt:



Scheme 1: Similarities between our previous results and our current attempt.

A general method for the functionalization of chromone at C-3 position usually involves lithiation followed by reaction with an electrophile or Heck coupling between 3-halochromenes and appropriate alkenes.[5,6] While both the aforementioned techniques work efficiently and provide ample flexibility for obtaining structurally diverse 3-substituted chromones, prior activation of the C-3 site can sometimes impact the overall yield of the reaction. Reaction at C-3 position by direct C-H functionalization using Pd(II) based complexes have also been reported by several research groups. Most of these approaches rely on nucleophilic attack of carbon-3 on Pd(II) catalyst as the first step to form C-3 palladated chromone, followed by subsequent step involving an appropriate coupling partner.[7] Kim et al., in their research efforts have reported palladium (II) catalyzed intermolecular alkenylation at the C-3 position of chromone.[8] Zhang and coworkers reported $Pd(OAc)_2$ catalyzed coupling of chromone with polyfluoroarenes.[9] Reaction was facilitated by the addition of excess amount of $^{i}Pr_2S$, which helped in improving the overall yield of the reaction. The developed protocol was also extended to other heteroatom-substituted enones. Hong and co-workers in a paper have reported the synthesis of benzofuran-fused chromones via C-3 selective functionalization of flavones and subsequent C-O cyclization. The reaction was catalyzed by $Zn(OTf)_2$ in the presence of $Cu(OAc)_2$.[10] The same group also reported formation of flavone-fused benzopyran moiety in the presence of catalytic system comprising of $Pd(acac)_2$, $Cu(OAc)_2$, Cs_2CO_3 and Al_2O_3.[11] Initially, the C-3 alkenylated chromone was generated, which subsequently underwent intramolecular cyclization to the target molecule. Zhao et al. has carried out C-3 sulfenylation of chromene using DMSO in the presence of NH_4I.[12] Patel and co-workers reported Fe-(III) catalyzed C-3 functionalization of flavone using *tert*-butyl peroxybenzoate (TBPB)/potassium persulphate ($K_2S_2O_8$) as oxidant combinations.[13]

For our project, none of the existing methods looked attractive as we wanted to avoid final step involving both pre-functionalization as well as C-H activation mediated direct C-C bond coupling. Given the inclusion of easy to oxidize aldehydes in the final step, we were particularly hesitant about using palladium-based catalysts as all the reported reactions also included stoichiometric amounts of additives as oxidants. As articulated previously, we decided to explore a Pictet-Spengler inspired approach for the synthesis of the target molecules. Accordingly, a reterosynthetic strategy was proposed as depicted in **Scheme 2**. Target molecule chromeno[3,2-*c*]quinolin-7-one **4** was supposed to be assembled from flavone **2** upon C-3 functionalization of the chromone ring. Intermediate **2** was to be sourced from easily accessible 2-(2-nitrophenyl)-4*H*-chromen-4-one **(1)** via reduction of its nitro functionality.



Scheme 2: Reterosynthetic analysis of 6-substituted chromeno[3,2-*c*]quinolin-7-one.

Results and Discussion

Our efforts started from the synthesis of 2-(2-nitrophenyl)-4*H*-chromen-4-one **(1a)** which was prepared using well-established literature protocols.[14] Subsequently, reduction of the nitro group with Fe/NH_4Cl lead to the formation of 2-(2-aminophenyl)-4*H*-chromen-4-one **(2a) (ESI)**. With compound **2a** in hand, efforts were focused on screening for appropriate conditions to generate the target molecules. Herein, the reaction between **2a** and benzaldehyde was used as the model reaction **(Table-1)**. Initially, reactions were attempted with diverse Lewis and Bronsted acids **(entry 1-6)**. While some of the reactions did not proceed beyond the formation of aldimines, however with $Yb(OTf)_3$ and $FeCl_3$ target molecules were obtained in 20% and 32% yields, respectively. Subsequent reactions **(entry 7-10)** were attempted with $FeCl_3$ to screen for the appropriate solvent. The reaction was successful only with nitrobenzene as a solvent, which gave compound **4a** in 56% yield. Further adjustment of the amount of catalyst did not improve the overall yield **(entry 11-12)**. Reactions when carried out with $FeCl_3$ (20 mol%) in the presence of various oxidizing agents such as TBPB, TBHP as well as in the combination of TBPB-Oxone or TBPB-$K_2S_2O_8$ did not result in the formation of the final product **(entry 13)**. Using $Fe(acac)_3$, as a catalyst **(entry 14)**, found suitable by Patel and co-workers in their synthetic studies on C-3 functionalization of flavones[13], did not yield the final product. When the reaction was attempted under air with $FeCl_3$ (20 mol%) as catalyst **(entry 15)**, fused chromeno-quinoline molecule was obtained in 44% yield. Thus, after thorough screening best results were obtained with 20 mol% $FeCl_3$ as catalyst and nitrobenzene as a solvent at 180 °C under nitrogen atmosphere **(entry 10)**.

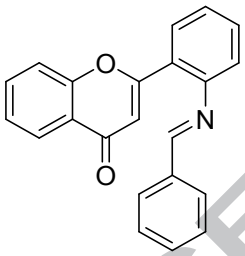
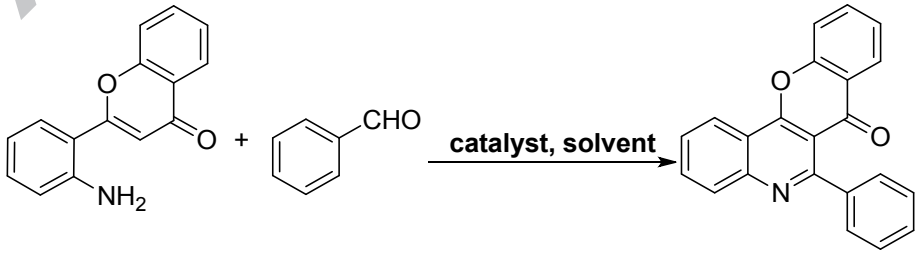


Figure 2: Structure of proposed aldimine intermediate.

Table 1: Screening of catalysts for the synthesis of chromeno[3,2-*c*]quinolin-7-one's.

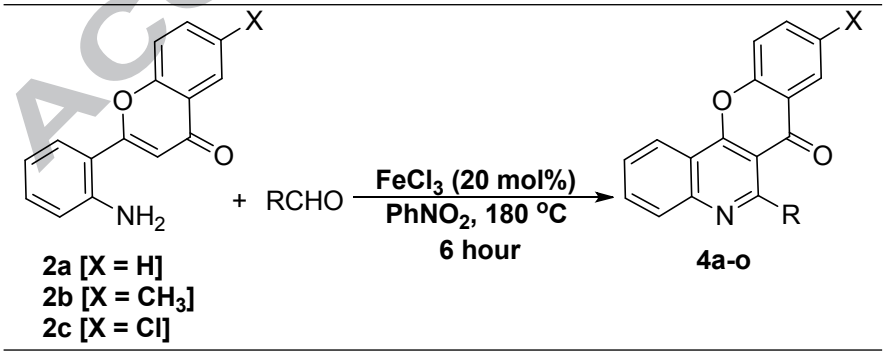


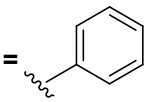
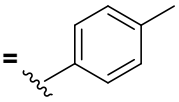
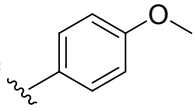
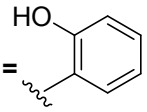
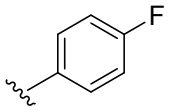
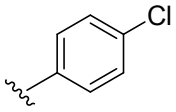
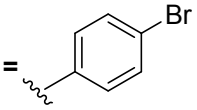
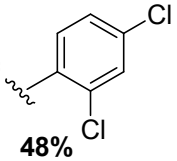
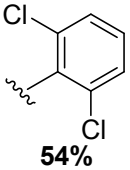
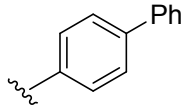
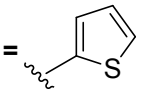
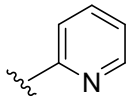
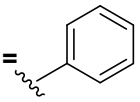
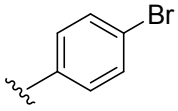
S.No.	Catalyst (20 mol%)	Solvent	Temp. (°C)	Time (in hr)	Yield (%)
1	PTSA	1,4-Dioxane	90	12	-
2	CF_3SO_3H	1,4-Dioxane	90	12	-
3	CH_3CO_2 H	-	110	12	-
4	$Yb(OTf)_3$	1,4-Dioxane	90	12	20
5	$Cu(OTf)_2$	1,4-Dioxane	90	12	-
6	$FeCl_3$	1,4-Dioxane	90	12	32
7	$FeCl_3$	DMF	140	12	-
8	$FeCl_3$	DMSO	140	12	-
9	$FeCl_3$	CH_3CN	90	12	-
10	$FeCl_3$	Nitrobenzene	180	6	56
11	$FeCl_3$[@]	Nitrobenzene	180	6	52
12	$FeCl_3$[#]	Nitrobenzene	180	6	56
13	$FeCl_3$[$%]	Nitrobenzene	180	12	-
14	$Fe(acac)_3$	Nitrobenzene	180	12	-
15	$FeCl_3$	Nitrobenzene	180	6	44[*]

All the reactions were carried out under nitrogen atmosphere unless mentioned; [*] reaction was carried out under air atmosphere; [@] Catalyst used 10 mol%; [#] catalyst used 30 mol%; [$]3 equivalents of oxidant such as TBPB (*tert*-butylperoxy-benzoate)/TBHP(*tert*-butylhydroperoxide)/oxone/$K_2S_2O_8$ were used along with the catalyst;[%] whenever two oxidants were used the ratio was 1:1(1.5 equivalents each).

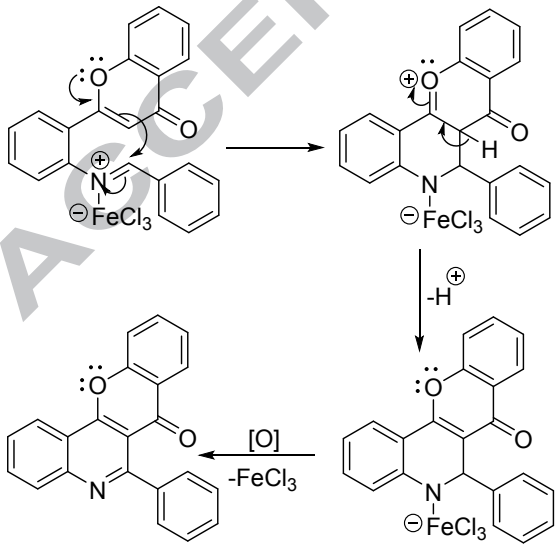
With optimized conditions in hand, we set out to demonstrate the substrate scope of the newly developed methodology. As shown in **Table 2**, wide array of aromatic aldehydes were examined in the synthesis of chromeno[3,2-*c*]quinolin-7-one **4a-o**. In general, aldehydes possessing electron donating groups (such as -OMe, -OH) resulted in moderate yields of the corresponding fused-chromeno products. Surprisingly, aldehyde bearing *p*-methyl group as the substituent gave comparatively better yield than the aforementioned aldehydes. Screening substrates with electron-withdrawing substitutions (e.g. F, Cl, Br) yielded the cyclized products in moderate to good yields. The yields were found to be effected by the electronegativity of the halogens. Best yield was obtained using *p*-fluorobenzaldehyde, whereas, the yield was compromised in the case of *p*-bromobenzaldehyde. Extending the scope of halogenated benzaldehydes to their di-chlorinated congeners yielded the target compounds in modest yield. Interestingly, more sterically hindered 2,6-dichlorobenzaldehyde gave better yield then its 2,4-disubstituted isomer. Subsequent reactions with *p*-phenylbenzaldehyde, thiophene-2-carboxaldehyde and pyridine-2-carboxaldehyde gave the final compounds in yields ranging from 25 to 47%. Scope of the reaction was also evaluated using 2-(2-aminophenyl)-6-methyl-4*H*-chromen-4-one and 2-(2-aminophenyl)-6-chloro-4*H*-chromen-4-one as substrates. Reaction carried out between 2-(2-aminophenyl)-6-methyl-4*H*-chromen-4-one and benzaldehyde, gave the corresponding chromeno[3,2-*c*]quinolin-7-one analogue in 45% yield, whereas with *p*-bromobenzaldehyde the yield of the final product was 40%. With 2-(2-aminophenyl)-6-chloro-4*H*-chromen-4-one and benzaldehyde as substrate the final product was obtained in 52% yield. Our attempts with aliphatic aldehydes (acetaldehyde, propionaldehyde, isovaleraldehyde and phenylacetaldehyde) were not fruitful and no products were obtained.

Table 2: Substrate screening



4a = 	**4b =** 	**4c =** 
56%	**61%**	**48%**
4d = 	**4e =** 	**4f =** 
37%	**65%**	**53%**
4g = 	**4h =** 	**4i =** 
52%	**48%**	**54%**
4j = 	**4k =** 	**4l =** 
35%	**47%**	**25%**
4m = 	**4n =** 	**4o =** 
X = CH_3	**X = CH_3**	**X = Cl**
45%	**40%**	**52%**

A plausible mechanism was proposed to rationalize the product formation. The reaction appears to proceed through cationic intermediate, similar to our previous observations **(Scheme-3)**.[4] The electrophilic attack of chromone ring *via* position 3 followed by oxidative aromatization are envisioned as key steps in the synthesis of the target molecules. An alternative mechanism, based on thermal 6π electrocyclization of imine intermediate followed by oxidative aromatization can also be considered. A similar mechanism was suggested by Khan *et al*. in order to rationalize the synthesis of coumarin fused quinolines/dihydroquinolines.[15]



Scheme 3: Plausible mechanism for the formation of the target molecule.

Relatively modest to low yields and the requirement of comparatively high reaction temperature, prompted us to study the putative aldiimine intermediate by DFT calculations. For this purpose the structure of the intermediate was optimized with the Gaussian 09 [DFT/cam-b3lyp/6-311++g(d,p)]. The optimized geometry was employed to calculate the Mulliken charge distribution, the HOMO and LUMO energy values **[See SI for details]**. The charge distribution showed comparable charges on the two reaction centers, which in our opinion rationalize the modest to low yields seen in the reaction.

Conclusions

In summary, we have developed a direct iron-catalyzed route involving functionalization of C-3 position of flavones for the synthesis of 6-substituted chromeno[3,2-*c*]quinolin-7-one. The developed method helps in coupling two C_{sp}^2 centers bearing similar charges and works with easily available aromatic aldehydes having electron rich and electron deficient substituents. Given the biological importance of flavones and quinolines, we feel that the devised method will find a lot of applications in the domain of medicinal chemistry. Additionally, since many chromone/flavone based natural products are C-3 substituted, the possibility of synthesizing these molecules without the aid of any additional activation or pre-functionalization step will prove to be an attractive feature.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Iron(III) catalyzed direct C-H functionalization at the C-3 position of chromone for the synthesis of fused chromeno-quinoline scaffolds

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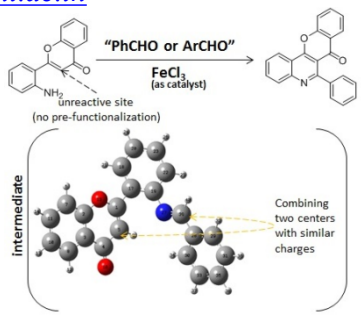

Highlights

- Functionalizing comparatively unreactive C-3 position of chromone
- Synthesis of hitherto unknown 6-substituted chromeno[3,2-*c*]quinolin-7-one's

- Final step without any additional activation or pre-functionalization