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FULL PAPER

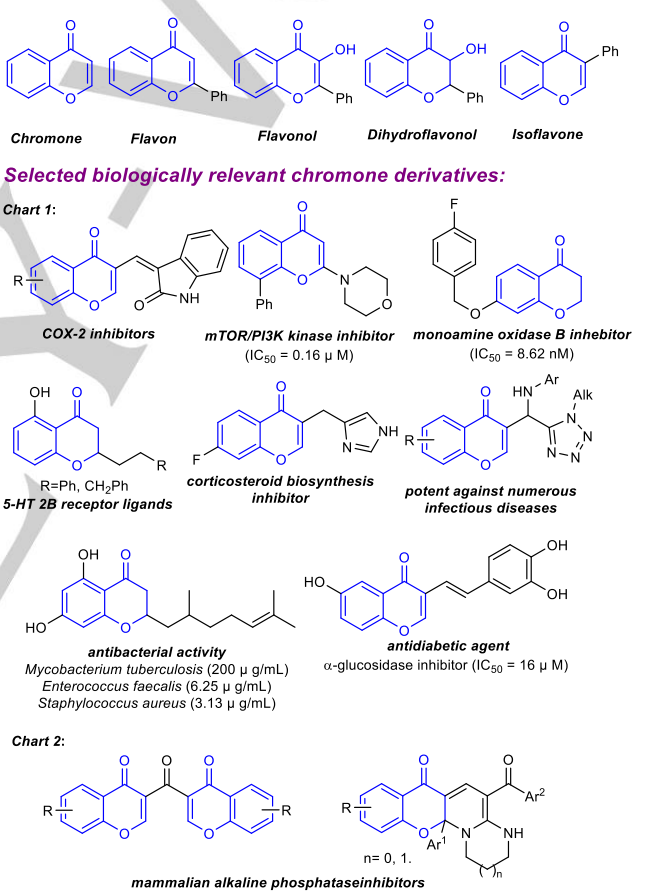
New entries to 3-acylchromones: TM- catalysed decarboxylative cross-coupling of α-keto acids with *ortho*-hydroxyarylenaminones, 2,3-unsubstituted chromones and 3-iodochromones.

Satenik Mkrtchyan,[a]* Viktor O. Iaroshenko,[a]*

Abstract: Herein we report three new synthetic routes for the construction of a 3-acyl-substituted chromone scaffold by employing an acylation of *ortho*-hydroxyarylenaminones, 2,3-unsubstituted chromones and 3-iodochromones through decarboxylative C-C cross-coupling with α-keto acids. This study indicates that the title transformations can be effectively catalysed by a set of silver and palladium salts. However, maximum efficiency in terms of overall yields was reported for the route starting from *ortho*-hydroxyarylenaminones. The scope of this methodology was thoroughly studied. It indicated a synthesis of 26 chromone derivatives in good to excellent yields.

Introduction

Chromones are naturally occurring oxygen-containing heterocyclic compounds that belong to the group of privileged scaffolds; the chromone core can be very often encountered as a structural part in numerous molecules with essential properties as well as in valuable biologically active compounds.[1] Chromone framework, as a structural fragment, is a part of flavonoids, such as flavones, flavonols, isoflavones etc (Scheme 1). The application of these compounds dates back to ancient times, traditional Asian and Middle Eastern medicine as part of phyto extracts and herbal cocktails. Biological and pharmacological profiles of chromone-containing molecules are vast and cover an impressive range of activities, among these are: topoisomerases inhibitors, protein tyrosine phosphatases inhibitors, phosphodiesterase inhibitors, leukotriene receptor antagonists etc (Scheme 1, Chart 1).[1b,2] The mentioned biological properties have been recently used for the development of numerous drugs and drug candidates based on chromone scaffold. For instance, anticancer drugs, anti-inflammatory drugs, mast cell-targeted drugs, antiplatelet drugs, drugs for neurodegenerative diseases, antimicrobial drugs, etc.[1b,2] Furthermore, several anti-obesity drug candidates containing chromone framework were discovered. On the other hand, plant flavonoids are commonly used to attenuate cardiovascular diseases. [3] Our recent studies indicated that the 3,3'-carbonyl-bischromones and pyridine fused chromone derivatives exhibit strong inhibition of phosphatase enzymes (Scheme 1, Chart 2).[4] Despite the impressive biological data available for chromones, this scaffold is of substantial interest for the design of advanced materials, mainly due to the prominent photophysical properties; Furthermore chromone scaffold can exhibit a wide range of colors.[1a, 5] Both photoemission and absorption are extensively used nowadays, this strongly influences the successful application of chromones for design and development of photoactive labels. [6, 7] Noteworthy, in the past two decades 3-hydroxyflavones better known as flavonols received much attention in this application. [6, 7]



Scheme 1. Chromone, flavonoids and biologically relevant compounds with chromone core.

Moreover, the chromone backbone, due to presence of the conjugated enone fragment, is a reactive synthon commonly used for the generation of more complex structural diversities following various synthetic routes.[8] Furthermore, 1,4-benzopyrone heterocyclic system, as a result of its reactivity, in retrosynthesis is often considered as masked 1,3-bielectrophile; in particular the structures furnished with electron withdrawing substituents in the position 3 are prone to undergo ANRORC reactions with

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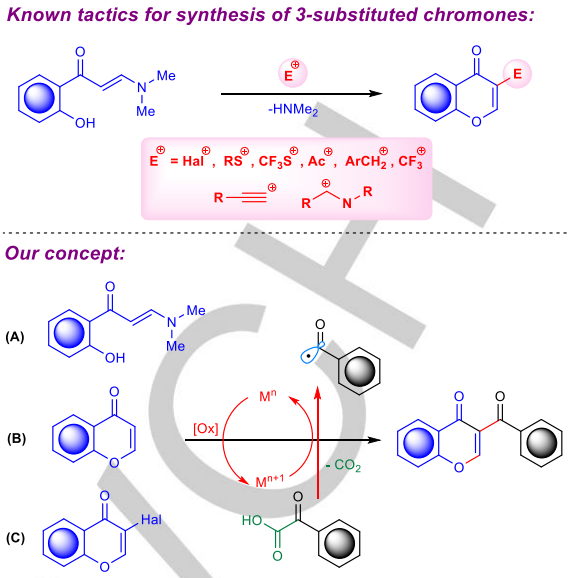
numerous dinucleophiles and thus are being used as versatile building blocks for constructing various heterocycles.[9]

The importance of biologically relevant chromone heterocyclic system has generated much attention in the past two decades fostering the development of synthetic protocols permitting an efficient, concise and straightforward synthesis of many chromone derivatives. [10] The presently available synthetic strategies often utilized for chromones preparation can be divided into two main synthetic tactics: (1) the functionalization/modification of naturally occurring or commercially available chromone derivatives by available synthetic means, [11, 12] (2) consecutive domino transformations enabling the rapid *in situ* construction of the chromone framework along with installation of various functional groups. [13] The first concept obviously has a major drawback, namely the limited pool of chromon substrates applicable for further synthetic modification along with the high costs of these precursors. Of note, synthetic tactics involving the *in situ* chromone ring construction are predominantly utilized for assembling 2-substituted products, since there is a limited number of routes able to provide 3-substituted chromones.[14]

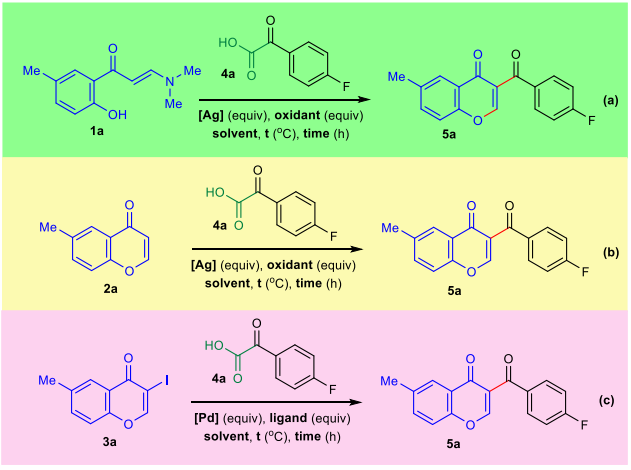
The synthesis of 3-substituted chromones very often involves reactions of *ortho*-hydroxyphenylenaminones with electrophiles or radicals, however this methodology was limited mainly to electrophiles, thus enabling an introduction of many functional groups, namely: acyl group, SR group and halogens along with fluorine (Scheme 2). [15, 16] Furthermore, this tactic was successfully utilized for the preparation of chromones containing various moieties in the position 3 such as CF_3, CF_2H, CF_2-R substituents,[17] SCF_3 group, [18] benzyls,[19] sulfenyl substituents, [20] phosphonic group. [21] At the same time, 3-alkynylchromones have found diverse applications in the construction of polycyclic heterocyclic systems [22], these compounds can be easily obtained through gold-catalysed tandem alkynylation/cyclization reaction of *ortho*-hydroxyarylenaminones using a TIPS-EBX as a suitable source for formal alkynyl cation. [23] A straightforward approach to 3-aminomethyl chromones was developed by Pan laboratory and involves three component reaction between *ortho*-hydroxyarylenaminones, aldehydes and urea in the presence of stoichiometric amount of water scavenger, namely the TMSCl. [24] In 2016 the groups of Suffert and Blond elaborated the synthesis of 3-alkyl chromones by using a vast range of alkyl iodides taken in 5 equiv. excess with stoichiometric amounts of AgOTf. [25] In 2006 Stevens et al. synthesised a set of 3-trimethylstanyl chromone derivatives using the hexamethyldistannane and utilized these valuable synthons to construct isoflavone skeleton through Migita–Kosugi–Stille coupling. [26] In 2017 our laboratory, being convinced in potential utility of these synthons, explored a reaction of *ortho*-hydroxyarylenaminones with hexamethyldisilane and hexamethyldigermane in TM-catalysed conditions expecting the formation of 3-(trimethylsilyl)- and 3-(trimethylgermyl)- chromones. We considered this scaffolds as promising low toxic building blocks for introducing a 3-chromyl moiety into complex organic molecules. Notwithstanding our extensive efforts, these synthetic routes experienced a failure. [27]

In the context of the mentioned *vide supra*, the development of a new practical methodology for synthesis of 3-substituted chromones is of considerable scientific interest.



Scheme 2. Synthesis of 3-substituted chromones: known data and our concept.

In the frames of our ongoing research program on the development of new efficient methods for the synthesis of 3-functionalized chromones we had a notion to employ a TM-catalysed decarboxylative cross-coupling of α-keto acids with *ortho*-hydroxyarylenaminones and 2,3-unsubstituted chromones aiming at efficient synthesis of 3-acylchromones (Scheme 2, routes A and B). On the other hand, we also speculated that the targeted drug-like scaffold can be achieved by the decarboxylative acylation/dehalogenation of 3-halogen chromones, as depicted in the route C of the Scheme 2. To the best of our knowledge, the proposed scenarios have not been brought to life to date. Thus, herein we report the overarching study aimed at the development and deployment of these three synthetic scenarios.



Scheme 3. Model reactions for reaction conditions optimization.

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Results and Discussion

In analogy to carboxylic acids serving as a suitable source for various alkyl and aryl groups in TM-catalysed decarboxylative arylations, α-keto acids are a valuable source for acyl groups. It is noteworthy that the α-keto acids, due to the availability of these compounds, are important synthons gaining broader application in organic synthesis for Ag-catalysed C−C bond formation through decarboxylative acylation[28], in particular being used for acyl functionalization diversities of heterocyclic and carbocyclic substrates. [29] In turn, Ag-catalysed tandem cyclization of linear double and triple bond containing aromatic substrates was also explored, and it is very often considered as an effective methodology for the construction of carbocyclic and heterocyclic frameworks. [30] In this context, the title transformations usually employ combination of Ag(I) salts, being the most efficient catalysts for this transformation so far, and $K_2S_2O_8$ as an efficient oxidant. The advantage of $K_2S_2O_8$ over its congeners is in the moderate solubility in many organic solvents which very often conditions its use as an oxidant of choice.

Regarding this as a base for reaction brings about optimization; the starting point of this study was to set up efficient conditions for the reaction between *ortho*-hydroxyarylenaminone **1a** and α-keto acid **4a** (Scheme 3a). Thus, we took several Ag-based catalytic systems adopted previously for decarboxylative acylation[28] and commenced by screening frequently changing variabilities such as solvent, additives, temperature and time of the reaction (Table 1, entries 1-12).

Table 1. Optimization of reaction conditions.

Reaction (a)[a]				
entry	oxidant (equiv)	catalyst (equiv)	solvent/ T/ time	yield (%) **5a**[d]
1	$Na_2S_2O_8$ (3)	Ag_2CO_3 (0.2)	DMSO:H_2O/60°C/12h	44
2	$Na_2S_2O_8$ (3)	AgOAc (0.2)	DMSO:H_2O/60°C/12h	69
3	$Na_2S_2O_8$ (3)	AgOAc (0.2)	DMSO:H_2O/60°C/24h	65
4	$Na_2S_2O_8$ (3)	AgOAc (0.2)	DMSO:H_2O/80°C/12h	50
5	**$Na_2S_2O_8$ (3)**	**AgF (0.2)**	**DMSO:H_2O/60°C/12h**	**85**
6	**$Na_2S_2O_8$ (3)**	**$AgNO_3$ (0.2)**	**DMSO:H_2O/60°C/12h**	**83**
7	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	DMSO/60°C/12h	52
8	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	acetone:H_2O/60°C/12h	47
9	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	THF:H_2O/60°C/12h	24
10	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	CH_3CN:H_2O/60°C/12h	28
11	---	$AgNO_3$ (0.2)	DMSO:H_2O/60°C/12h	-
12	$Na_2S_2O_8$ (3)	---	DMSO:H_2O/60°C/12h	-
Reaction (b)[b]				
13	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	DMSO/100°C/12h	29
14	$Na_2S_2O_8$ (3)	$AgNO_3$ (0.2)	DMSO:H_2O /100°C/12h	45
15	**$Na_2S_2O_8$ (3)**	**$AgNO_3$ (0.2)**	**DMSO:H_2O/100°C/16h**	**65**
16	**$Na_2S_2O_8$ (3)**	**AgF (0.2)**	**DMSO:H_2O/100°C/16h**	**67**
17	---	$AgNO_3$ (0.2)	DMSO:H_2O/100°C/16h	-
18	$Na_2S_2O_8$ (3)	---	DMSO:H_2O/100°C/16h	-
Reaction (c)[c]				
entry	additives	catalyst/ligand (equiv)	solvent/ T/ time	yield (%) **5a**[b]
19	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) / P(*o*-Tol)$_3$ (0.05)	Toluene/130 °C/20h, under Ar	24
20	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) /dppf(0.05)	Toluene/130 °C/20h, under Ar	28
21	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) /dppf (0.05)	DMF/130 °C/20h, under Ar	44
22	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) /Xantphos (0.05)	DMF/130 °C/20h, under Ar	27
23	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) / dppe (0.05)	DMF/130 °C/20h, under Ar	10
24	**CsF(1.5)/CuI(0.15) /phen(0.2)**	**$Pd(OAc)_2$ (0.03) /dppp(0.05)**	**DMF/130 °C/20h, under Ar**	**51**
25	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(TFA)_2$(0.03) /dppp(0.05)	DMF/130 °C/20h, under Ar	50
26	KF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) /dppp(0.05)	DMF/130 °C/20h, under Ar	12

27	CsF(1.5)/CuI(0.15) /phen(0.2)	$Pd(OAc)_2$ (0.03) /dppb(0.05)	DMF/130 °C/20h, under Ar	30
28	CsF(1.5)/CuI(0.15) /phen(0.2)	$Ni(OAc)_2$ (0.03) /dppp(0.05)	DMF/130 °C/20h, under Ar	23

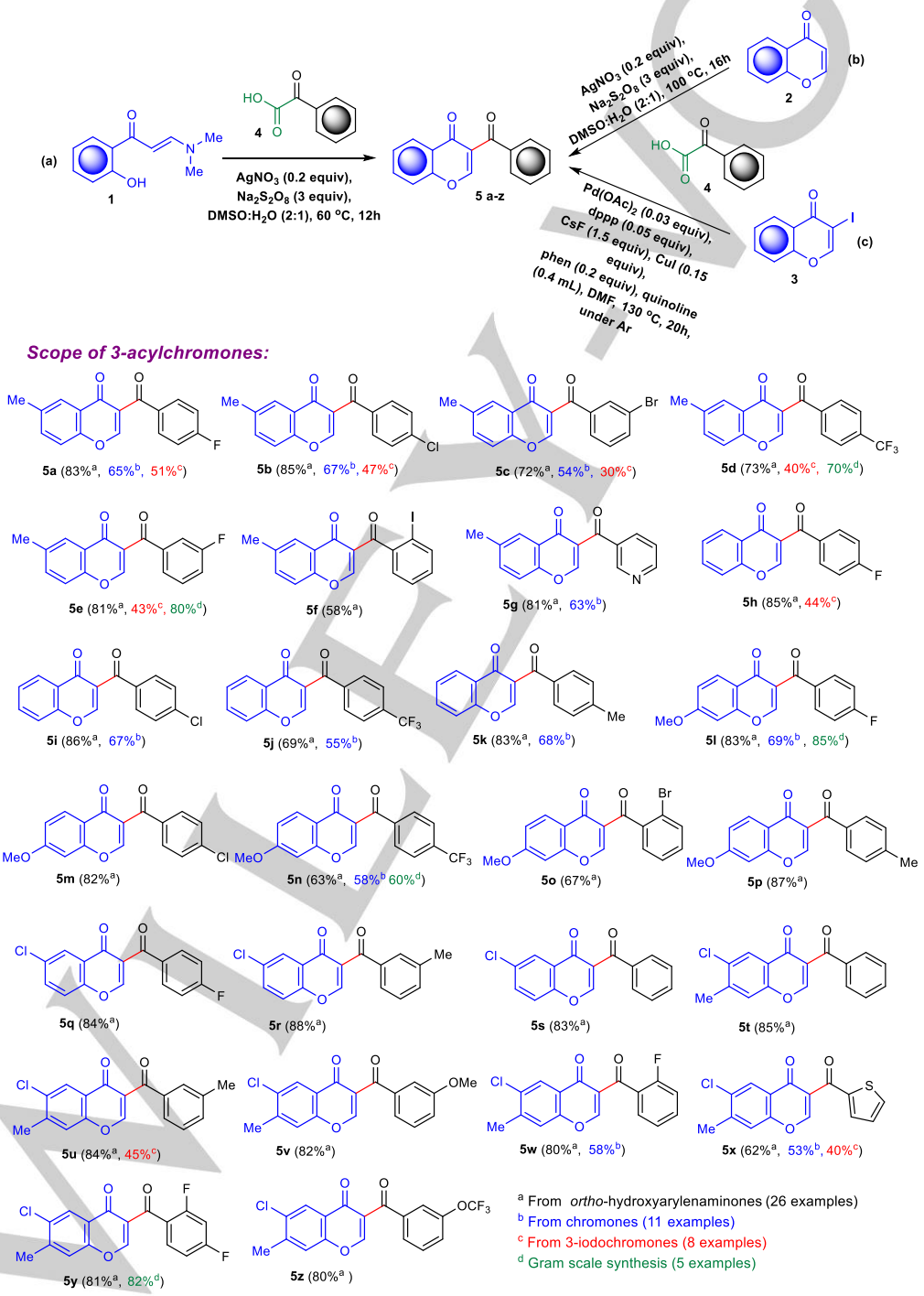
[a] Reaction conditions: **1a** (0.1 mmol) and **4a** (0.14 mmol) in DMSO:H_2O solvents (v/v = 2:1, 4 mL). [b] Reaction conditions: **2a** (0.1 mmol) and **4a** (0.14 mmol) in DMSO:H_2O solvents (v/v = 2:1, v/v = 2:1, 4 mL).[c] Reaction conditions: under Ar, **3a** (0.1 mmol) and **4a** (0.12 mmol) in dry DMF (2.5 mL) and dry quinolone (0.4mL). [d] Isolated yields after column chromatography on silica gel.

We screened a range of commercial silver salts and we revealed that AgF and $AgNO_3$ exerted optimal efficiency as catalysts leading to the formation of the corresponding chromone product **5a** in 85% and 83% respectively (Table 1, entries 5, 6). In addition to the experiments depicted in the Table 1 we have studied a vast range of other commercial Ag(I) salts, among those are: $AgBF_4$, $AgPF_6$, Ag_2O, AgOTf, AgCl, however the performance of these catalysts were rather insufficient. In the course of preliminary screenings, we also focused on the evaluation of different bases. Of note, the addition of a base, in particular commonly used carbonates or acetates, usually either hampered the reaction or substantially decreased the efficiency. Due to its efficiency and its availability, we decided to use commercial $AgNO_3$ for further development of this chemistry. Obviously, the reaction was highly solvent- and temperature-dependent, the mixture DMSO/H_2O 2:1 was established as the best reaction media over other frequently used solvents, and the 60 °C as optimal reaction temperature. Increasing or decreasing the reaction temperature usually resulted in lower yields. Subsequently, we found that the reaction reached its completion within 12 hours. Finally, we successfully formulated the optimal reaction conditions which consisted in the use of 0.2 equiv. of $AgNO_3$, 3 equiv. of $K_2S_2O_8$ as an oxidant and mixture DMSO/H_2O 2:1 as a solvent, with 1.4 excess of the corresponding α-keto acid (Table 1, entry 6). The excess of the acid coupling partner is essential since acid is also consumed for simultaneous formation of carboxylic acid by-product, which was always detected over the course of the reaction. As for the acylation of 2,3-unsubstituted chromones illustrated in the Scheme 3b, the optimal conditions of entries 5 and 6 did not work in this case. However, when we increased the temperature to 100 °C and extended the reaction duration to 16 h we observed the formation of the expected chromone product in 65 % yield using $AgNO_3$ and in 67% yield using AgF respectively (entries 15, 16). Increasing the temperature up to 110 °C and finally to 130 °C did not have any visible effect on the yields. Substitution of DMSO/H_2O 2:1 solvents mixture with DMSO had quite a negative effect on the reaction efficiency of both model reactions (entries 7, 13). The observations showed that Ag(I) salt and $K_2S_2O_8$ are indispensable for both described protocols, no reaction was observed in the absence of any of these components (Table 1, entries 11, 12, 17, 18).

Optimal reaction conditions developed for the reaction of the Schemes 3a and 3b were not suitable to transform 3-halogen chromones to the targeted 3-acylchromones, thus as a starting point for this route we have chosen the reaction conditions published by Goossen group for Cu/Pd- catalysed decarboxylative couplings of aryl halides with α-keto acid. [31] First we tried to reproduce the original procedures which indeed gave rise to the formation of the desired product, however the title transformation was accompanied by the intensive dehalogenation of the corresponding 3-iodochromone **3a** delivering the 2,3-unsubstituted chromone **2a** as a main product. After modification we formulated new reaction conditions entailed in using toluene as reaction media, $Pd(OAc)_2$ as catalysts, P(*o*-Tol)$_3$ as ligand, we also used CuI as a co-catalyst with 1,10-phenanthroline as a ligand, along with 1,5 equiv. of CsF. The latest conditions allowed us to obtain the compound **5a** in 24 % yield (entry 19). Substitution of toluene for DMF with dppf ligand slightly improved the yield (entry 21). Subsequently, we screened several combinations of Pd(II), Ni(II) and Cu(I, II) salts, as well as a range of commercial bidentate phosphine ligands, such as dppp, dppe, dppf and xantphos. Selected entries of the optimisation study are depicted in the Table1 (entries 20-28). Remarkably, utilisation of $Pd(OAc)_2$, CuI and dppp phosphine ligand with the rest of reaction components remained unchanged, increased the yield to 51% (entry 24). Substitution of CsF with KF resulted in substantial decrease of the yield. Despite the mentioned conditions we evaluated several other catalytic systems based on the combination of Ag(I) salts with Pd(II) catalysts [32] which unfortunately did not deliver the projected results. Other chromone halides bearing chlorine and bromine atoms in the position 3 were also tested, however, those chromone substrates were not reactive. Of note, $Ni(OAc)_2$ was prone to catalyse the reaction but the efficiency was rather low.

We decided to compare the efficiency of all three developed synthetic protocols and started with the evaluation of the route depicted in the Scheme 3a. With the optimal reaction conditions for these new synthetic scenarios in hand we focused next on the elaboration of the scope and limitation of this reaction by using the conditions of the entry 6 taking $AgNO_3$ as a catalyst. In order to study the scope, we selected five *ortho*-hydroxyarylenaminones **1** obtained from commercial 2'-hydroxyacetophenones, and sixteen α-keto acids **4** which can be prepared from structurally related commercial acetophenones utilizing the SeO_2 oxidation reaction,[33] and reacted these species under optimized reaction conditions. This study resulted in the preparation of a 26-compounds library of corresponding 3-acyl-substituted chromones **5a-z** shown in the Scheme 4. Noteworthy, α-keto acid substrates **4** with both electron-donating and electron –withdrawing substituents at the benzene ring as well as 2-thienyl and 3-pyridyl heterocyclic moieties were successfully utilized for the preparation of the targeted chromone derivatives. In all cases the title acylation reaction proceeded smoothly and provided the corresponding products **5a–z** in moderate to excellent yields. However, our observations indicated that the electronic effect caused by substituents placed in *ortho*- and *para*- positions has a visible impact on the efficiency of the reaction. Namely: (1) the presence of electron-donating groups at the *para*-position of the phenyl substituent is leading to higher yields; (2) at the same time, placing electron-withdrawing groups at the *para*-position visibly reduces the reaction efficiency by decreasing the yields. Of note, substituents in the *meta*-position did not have any visible effect. Acid substrates bearing bromine and iodine substituents usually showed lower yields in comparison with corresponding

chlorinated and fluorinated derivatives. For bromo and iodo derivatives the reaction was usually accompanied by intensive dehalogenation, this in turn is a reason for low yields. Regarding the heterocyclic α-keto acids, it is important to mention that the 3-pyridine derivative **5g** showed a favorable yield, in contrary to the case of the 2-thienyl α-keto acid we observed distortion in terms of yields, thus the chromone derivative **5x** was obtained in rather low yield of 62%. This methodology also demonstrated excellent scalability, as a result five compounds were prepared in multi-gram quantities. As for the protocols depicted in the Schemes 3b and 3c, by using the optimized reaction conditions (Table 1, entries 15 and 24) we prepared eleven and eight compounds in good and fair yields respectively. The results are summarized in the Scheme 4. Compared with the reaction in the Scheme 3a, these two synthetic routes displayed rather average and low efficiency respectively.



Scheme 4. Substrate scope for the synthesis of 3-acylchromones by reaction with different α-keto acids.

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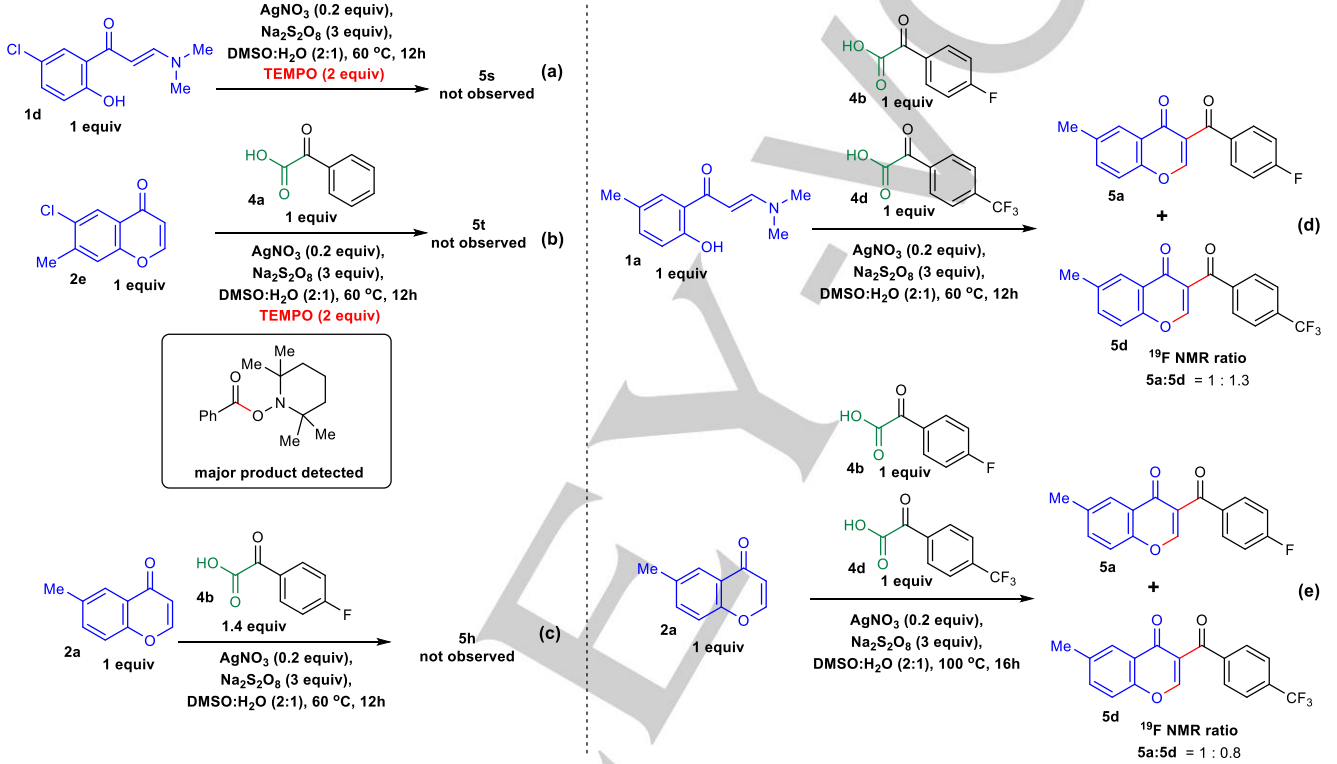
To gain insights into the mechanism of the decarboxylative acylation of *ortho*-hydroxyarylenaminones and 2,3-unsubstituted chromones, several control experiments were performed (Scheme 5). First, the addition of 2 equiv. of TEMPO completely hampered the acylation of both substrates and simultaneously we detected the formation of acyl-captured TEMPO, demonstrating the involvement of radical species in the synthetic routes to 3-acylchromones (Schemes 5a, 5b). We expected the acylation of the *ortho*-hydroxyarylenaminones to entail initial cyclization of enaminone species into chromone. However, the formation of the chromone moiety was not observed. Furthermore, the acylation of chromone depicted in the Scheme 5c under standard reaction conditions experienced a failure. The outcome of this experiment might be accepted as an evidence supporting the postulated mechanism which involves the immediate attack of the acyl radical onto the *ortho*-hydroxyarylenaminone framework. Finally, two competitive reactions between enaminone **1a**, chromone **2a** and fluorinated α-keto acids **4b** and **4d**, furnished with either fluorine atom or CF_3 group in the *para*-position respectively, were conducted. Analysis of reaction mixtures by ^{19}F NMR revealed that 1equiv. of the enaminone **1a** reacted with the mixture of 1 equiv. of acid **4b** and 1 equiv. of acid **4d** giving rise to a mixture of corresponding chromones in the 1:1.3 ratio (Scheme 5d). In contrary, the same reaction for chromone **2a** delivered the corresponding mixture in the 1:0.8 ratio (Scheme 5e).



Scheme 5. Control experiments. (a, b): Reactions with 2 equiv. of TEMPO; (c) Attempt to prove 2,3-unsubstituted chromones as possible intermediates; (d, e): Competitive experiments between *ortho*-hydroxyarylenaminone, chromone and two fluorinated α-keto acids.

Having in mind the extensive literature data on the decarboxilative acylation by α-keto acids and results obtained by control experiments, we assumed that these transformations also in the case of Ag-catalysed decarboxylative cross-coupling of α-keto acids with *ortho*-hydroxyarylenaminones and the 2,3-unsubstituted chromone ring system should proceed as radical process involving the described hitherto formation of the acyl radical intermediates, which in turn reacts with an appropriate substrate. Noteworthy, taking into account previous precedents known in the literature we proposed a feasible reaction mechanism for *ortho*-hydroxyarylenaminones which is depicted in the Scheme 6a. The postulated sequence encompasses five main steps: (1) formation of acyl radical by the oxidative decarboxylation of α-keto acid; followed by (2) the addition of the acyl radical, generated *in situ,* on the enaminone delivering the corresponding radical intermediate **6**; which subsequently undergoes (3) oxidation affording the corresponding iminium intermediate **7**; the concomitant (4) γ-pyrone ring formation delivers the oxonium species **8**; and finally, (5) subsequent deprotonation and elimination of dimethylamine furnishes the desired 3-acylchromone framework. The precedential formation of iminium intermediates of such sort was previously described by Chen and Yang in their seminal work devoted to the visible-light-driven synthesis of 3-CF_2/CF_3-containing chromones from *ortho*-hydroxyarylenaminones. [17a] On the other hand, the reverse sequence of steps (3) and (4) is also possible, in particular the γ-pyrone ring formation which gives rise to the corresponding O-centered protonated radical species can occur prior to the oxidation event. This actually does not contradict the general chemical logic. The acylation of chromones at the position 3 most probably involves the initial formation of the O-acylated radical chromone adduct which then after oxidation into the O-acyl pyrilium moiety undergoes Fries-type rearrangement followed by the loss of the proton and finally results in the 3-acylchromone scaffold (Scheme 6b). The O-acylated radical chromone intermediate can in turn undergo the postulated rearrangement accomplished by the subsequent oxidation of the newly formed radial species. Another plausible pathway could involve the

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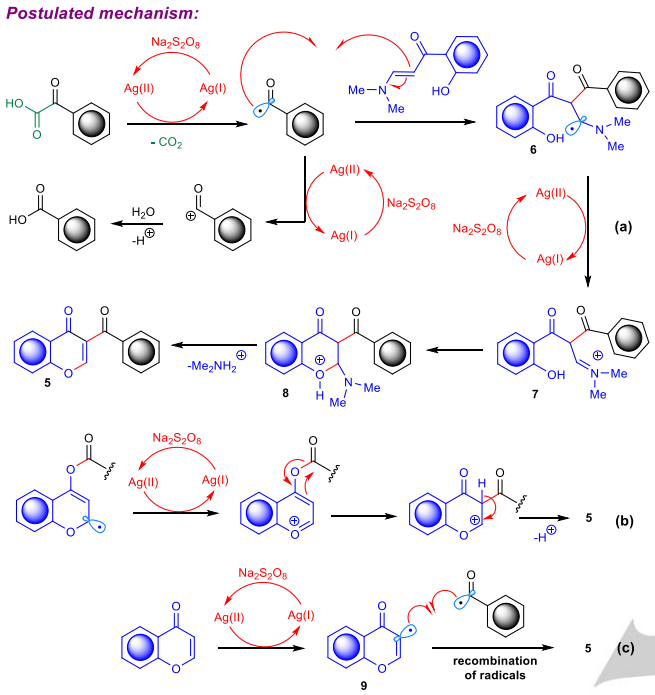
formation the chromone radical **9** followed by reaction with acyl radical (Scheme 6c). This pathway however shall be accompanied by the formation of several typical for this pathway by-products like 3-hydroxychromones and 3,3'-bichromones. Of note, we could not detect any of those species.



Scheme 6. Proposed catalytic cycle for decarboxilative acylation of *ortho*-hydroxyarylenaminones and 2,3-unsubstituted chromones.

Conclusions

In summary, we have developed a new, challenging, straightforward methodology for the synthesis of vast diversity of 3-acylchromones by direct acylation of *ortho*-hydroxyenaminones utilizing popular in recent years Ag- catalysed decarboxylative cross-coupling of α-keto acids. We compared the efficiency of this methodology with two other protocols which use 2,3-unsubstituted chromones and 3-iodochromones as substrates. The Ag-mediated acylation of 2,3-unsubstituted chromones showcased good yields. This strategy, utilizing 3-iodochromones, cannot be denoted as a feasible preparative method due to its rather insufficient performance. In general, the acylation of *ortho*-hydroxyenaminones showcased high yields which strongly depend upon the electron-donating/withdrawing nature of the Ar residue of the α-keto acid. Scalability of this synthetic protocol was also demonstrated by the preparation of five compounds in gram quantities. As quintessential, the mechanistic studies were undertaken, which helped us to postulate plausible mechanistic sequences.

Experimental Section

Commercially available starting materials, reagents, catalysts and anhydrous and degassed solvents were used without further purification. Flash column chromatography was performed with Merck Silica gel 60 (230-400 mesh). The solvents for column chromatography were distilled before the use. Thin layer chromatography was carried out using Merck TLC Silica gel 60 F_{254} and visualized by short-wavelength ultraviolet light or by treatment with potassium permanganate ($KMnO_4$) stain. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 250 and 500 MHz at 20°C. All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm) and DMSO (2.50 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77.00 ppm) or DMSO (39.70 ppm) and were obtained with ^1H decoupling. Coupling constants, *J*, are reported in Hertz (Hz). Gas chromatographic analyses was performed on Gas Chromatograph Mass Spectrometer GCMS-QP2010 Ultra instrument.

The optimal reaction conditions were identified by Microscale High-Throughput Experimentation Screening. Parallel synthesis was accomplished in an MBraun glovebox operating with a constant Ar-purge (oxygen and water <5 ppm). Screening reactions were carried out in 4-18 mL Ace Pressure Tubes using suitable heating blocks. Liquid chemicals were dosed using gas tight micro syringes. Isolation of obtained compounds was achieved by column chromatography on Silica gel.

General procedure for the synthesis of 3-acylchromones by Ag-catalyzed decarboxylative cross-coupling of α-keto acids with *ortho*-hydroxyarylenaminones. Synthesis of compounds 5a-z.

Under inert atmosphere (glovebox operating with a constant Ar-purge) corresponding *ortho*-hydroxyenaminone **1** (1 mmol), an appropriate α-keto acid **4** (1.4 mmol), $K_2S_2O_8$ (3 mmol), $AgNO_3$ (0.2 mmol) were weighed and successively placed into an Ace Pressure Tube equipped with a magnetic stir bar, which then was capped with a stopper. Subsequently, the pressure tube was taken out of the glovebox and loaded with 4 mL of DMSO:H_2O mixture (v/v = 2:1). Afterwards, the reaction mixture was vigorously mixed and heated at 60°C for approximately 12h, the progress of the reaction was controlled by TLC. Upon completion, the reaction was cooled to room temperature, treated with 5mL of MeOH, transferred to a round bottom flask and concentrated using rotary evaporator under vacuum, then was kept on oil vacuum pump (approximately at $2x10^{-4}$ unit). The crude mass was washed with water, filtrated and dried. The residue was purified by preparative column chromatography on Silica gel typically using hexane/ethyl acetate mixtures to provide the desired chromone derivative. The gram synthesis of compounds **5d, 5e, 5l, 5n, 5y** was accomplished starting from 0.02 mol of the appropriate *ortho*-hydroxyarylenaminones.

General procedure for the synthesis of 3-acylchromones by Ag-catalyzed decarboxylative cross-coupling of α-keto acids with 2,3-unsubstituted chromones. Synthesis of compounds 5a-c, 5g, 5i-l, 5n, 5w, 5x.

Under inert atmosphere (glovebox operating with a constant Ar-purge) corresponding 2,3-unsubstituted chromone **2** (1 mmol), an appropriate α-keto acid **4** (1.4 mmol), $K_2S_2O_8$ (3 mmol), $AgNO_3$ (0.2 mmol) were weighed and successively placed into an Ace Pressure Tube equipped with a magnetic stir bar, which then was capped with a stopper. Subsequently, the pressure tube was taken out of the glovebox and loaded with 4 mL of DMSO:H_2O mixture (v/v = 2:1). Afterwards, the reaction mixture was vigorously mixed and heated at 100°C for approximately 16h, the progress of the reaction was controlled by TLC. Upon completion, the reaction was cooled to room temperature, treated with 5mL of MeOH, transferred to a round bottom flask and concentrated on rotary evaporator under vacuum, then was kept on oil vacuum pump (approximately at 2x10-

[4] unit). The crude mass was washed with water, filtrated and dried. The residue was purified by preparative column chromatography on Silica gel typically using hexane/ethyl acetate mixtures to provide the desired chromone derivative.

General procedure for the synthesis of 3-acylchromones by Pd-catalyzed decarboxylative cross-coupling of α-keto acids with 3-iodochromones. Synthesis of compounds 5a-e, 5h, 5u, 5x.

Under inert atmosphere (glovebox operating with a constant Ar-purge) corresponding 3-iodochromon **3** (0.1 mmol), CsF (1.5 mmol), an appropriate α-keto acid **4** (1.2 mmol), CuI (0.15 mmol), 1,10-phenanthroline (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.05 mmol) were weighed and placed successively into an Ace Pressure Tube equipped with a magnetic stir bar. Finally, 2.5 mL of dry DMF and 0.4 mL of dry quinolone were added inside the glovebox, then the reaction vessel was capped with a stopper. Subsequently, the pressure tube was taken out of the glovebox and heated at 130°C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and concentrated under vacuum. The crude mass was washed with water, filtrated and dried. The residue was purified by preparative column chromatography on Silica gel typically using hexane/ethyl acetate mixtures to provide the desired chromone derivative.

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Keywords: Acylation, C-C Coupling, Catalysis, Heterocycles, Chromones.

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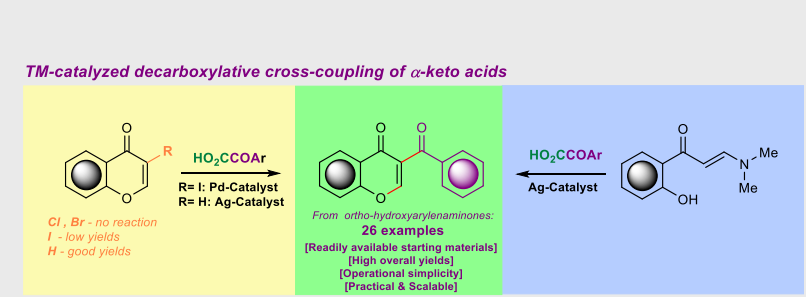

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New entries to 3-acylchromones: TM-catalysed decarboxylative cross-coupling of α-keto acids with *ortho*-hydroxyarylenaminones, 2,3-unsubstituted chromones and 3-iodochromones.

Key Topic:
Chromone Chemistry

TOC Text:
Three new entries to 3-acylchromones utilising transition metal catalysed decarboxylative cross-coupling reactions of α-keto acids with *ortho*-hydroxyenaminones, 2,3-unsubstituted chromones and 3-iodochromones are reported. The title methodologies permit a concise synthesis of series of drug-like chromone derivatives and are suitable for the combinatorial preparation of compounds libraries.