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A simple and convenient synthesis of 3-salicyloylquinoline-4-carboxylic esters from chromone and isatin†

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A simple and convenient synthesis of 3-salicyloylquinoline-4-carboxylic esters has been developed through an $AlCl_3$-catalyzed reaction of easily available Baylis–Hillman adducts from chromones and isatin-derivatives. This reaction involves esterification, cyclization and ring opening in a one-step process, and provides an efficient approach for easy access to a series of valuable salicyloylquinoline derivatives with high yields. Moreover, this protocol offers several advantages, such as availability of starting materials, economic availability, operational simplicity and mild reaction conditions.

Introduction

Quinoline motifs are important subunits of many drugs and natural products, and are ubiquitous in nature.[1] These classes of compounds exhibit a wide range of remarkable biological and pharmacological activities such as anti-microbial,[2] anti-cancer,[3] anti-tubercular,[4] anti-plasmodial,[5] anti-malarial,[6] anti-trypanosomal,[7] anti-HIV,[8] anti-inflammatory[9] and anti-psoriasis[10] activities.

Groups such as salicyloyl, present in some active natural products, are associated with significant biological properties.[11] Therefore, introduction of a salicyloyl group into a molecular structure has been a useful strategy in structural modifications of heterocyclic compounds, and has made brilliant achievements in the structure modification of pyridine,[12] benzofuran,[13] indole,[14] coumarin[15] and pyrrole.[16] Most of these compounds display potent biological properties, including anti-tumor,[17] anti-bacterial,[18] photo-antioxidant,[19] anti-mitotic and anti-vascular[14] activities; they could also act as SIRT1 inhibitors[13] (Fig. 1). Presently, several methods have been developed to assemble heterocyclic compounds with salicyloyl group.[20] However, the reports about the construction of salicyloylquinoline are seldom, and the structural diversity is limited by the choice of starting materials. The approaches for salicyloylquinoline include TMSCl-mediated cyclization of 3-formylchromone with various anilines[21] and aromatic nitro-group reduction of Baylis–Hillman alcohols from chromones and 2-nitrobenzaldehydes.[22]

In view of the significance and utility both quinoline and salicyloyl group, there is considerable interest in exploring novel synthetic approaches to various salicyloylquinoline from common, commercially available starting materials.

Chromones are used as building blocks for constructing various biological heterocycles. The application of chromone in the synthesis of salicyloyl-heterocycles has previously been reported.[23] Interestingly, chromones can act as novel activated alkenes in the Baylis–Hillman coupling with isatin-derivatives, heteroaromatic-aldehydes and nitrobenzaldehydes. Meanwhile, the Baylis–Hillman adducts can be transformed into

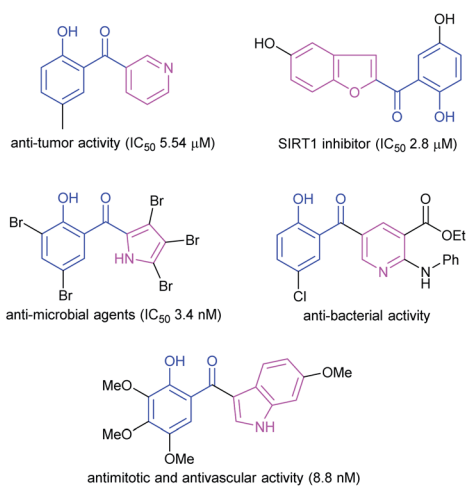

Fig. 1 Representative examples of salicyloylheterocycles.

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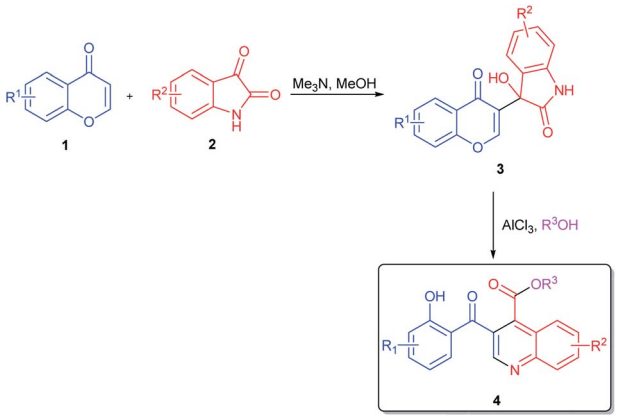


Scheme 1 Synthesis of 3-salicyloylquinoline-4-carboxylic esters.

heterocyclic framework.[24] Based on the above studies, and our ongoing interesting in constructing salicyloylquinoline, we report a simple and convenient protocol for the synthesis of 3-salicyloylquinoline-4-carboxylic esters from the Baylis–Hillman adducts of chromones and isatin-derivatives (Scheme 1).

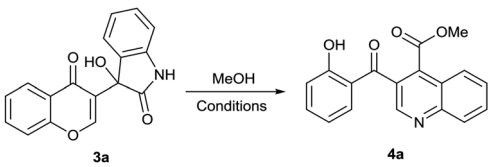
Results and discussion

3-Salicyloylquinoline-4-carboxylic esters were synthesized as shown in Scheme 1. Chromones were coupled with isatin-derivatives through Baylis–Hillman reaction in the presence of methanolic trimethylamine (25% w/w) to generate 3-hydroxy-3-(4-oxo-4*H*-chromen-3-yl)indolin-2-ones **3**.[24] With the Baylis–Hillman adducts **3** on hand, our efforts focused on transforming from **3** to **4**. To optimize the reaction conditions, we examined a variety of acid catalysts taking the reaction of **3a** with methanol as a model. The results were listed in the Table 1.

As shown in Table 1, different types of acids, such as $ZnCl_2$, TFA, TMSCl, TfOH and HCl were employed as catalysts, but only TMSCl, TfOH and HCl afforded trace amounts of the desired product **4a** (Table 1, entry 1–5). To our delight, when $AlCl_3$ (0.5 equiv.) was used, compound **4a** was obtained in a yield of 54% (Table 1, entry 6). In order to improve the efficiency of the reaction, different amounts of $AlCl_3$ were investigated (Table 1, entry 7 and 8), and the investigation indicated that the optimal amount of catalyst was $AlCl_3$ with 1 equiv. in 85% yield (Table 1, entry 8).

Under the above optimum reaction conditions, we tested the substrate scope for the synthesis of 3-salicyloylquinoline-4-

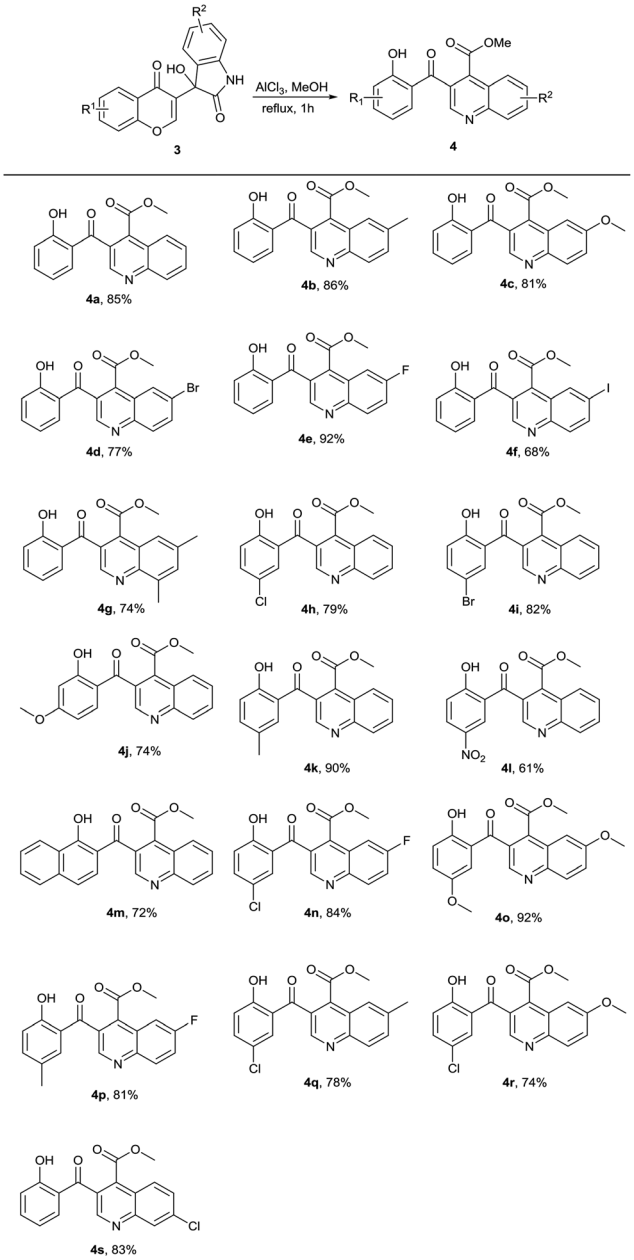
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (equiv.)	Time (h)	Yield[b] (%)
1	TMSCl (0.5)	1	Trace
2	TfOH (0.5)	1	Trace
3	TFA (0.5)	1	n.d.[c]
4	HCl (0.5)	1	Trace
5	$ZnCl_2$ (0.5)	1	n.d.
6	$AlCl_3$ (0.5)	1	54%
7	$AlCl_3$ (0.7)	1	71%
8	$AlCl_3$ (1.0)	1	85%

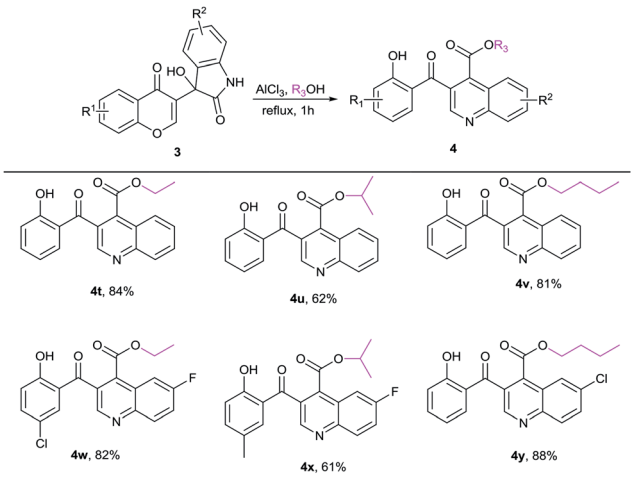
[a] Reaction conditions: **3a** (0.5 mmol) and methanol (3 mL) at reflux under air. [b] Isolated yield. [c] Not detected.

Table 2 Scope of the reaction of **3** with MeOH[a,b]



[a] Reaction conditions: **3** (0.5 mmol) and $AlCl_3$ (0.5 mmol) in methanol (3 mL) at reflux under air for 1 h. [b] Isolated yield.

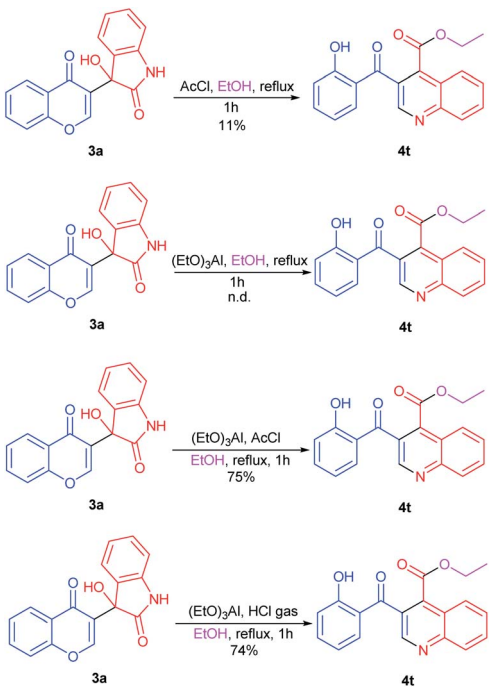
Table 3 Scope of the reaction of alcohol with **3**[a,b]



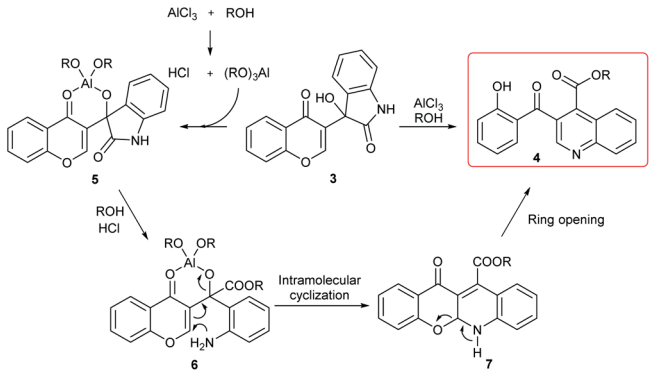
[a] Reaction conditions: **3** (0.5 mmol) and $AlCl_3$ (0.5 mmol) in alcohol (3 mL) at reflux under air for 1 h. [b] Isolated yield.

carboxylic esters **4**. Firstly, a range of 3-hydroxy-3-(4-oxo-4*H*-chromen-3-yl)indolin-2-ones **3** were investigated, and the representative results were listed in Table 2. Baylis–Hillman adducts **3** with various R_1 or R_2 group in MeOH proceeded smoothly to afford the desired products in good yields with 61–92% (**4a–4s**).

Moreover, the reactivity of alcohol was also tested, and the results were shown in Table 3. The structures of alcohols showed little impact on the results.



Scheme 2 Control experiments.



Scheme 3 Proposed mechanisms.

In order to probe the mechanism of this reaction, control experiments were further carried out (Scheme 2). The reactions were conducted under acetyl chloride and triethoxyaluminum respectively. The results showed that the **4t** was obtained in 11% yield with 3 equiv. of HCl which generated from acetyl chloride with alcohol. And in the presence of triethoxyaluminum, the product **4t** was not detected. However, when acetyl chloride (3 equiv.) and triethoxyaluminum (1 equiv.) were added simultaneously, the reaction proceeded smoothly and afforded **4t** in 75% yield. Meanwhile, reaction of **3a** with triethoxyaluminum in EtOH was tested in the presence of HCl gas. The reaction proceeded smoothly to afford the desired product in 74% yield. This result indicates that the formation of **4** was based on the cooperative effect of HCl and aluminum alkoxides.

On the basis of the above observations and the previously literature reports,[22,25] a plausible mechanism for the formation of **4** is presented in Scheme 3. The initial step involves the alcohol exchange and coordination of **3** with aluminum alkoxides to generate intermediate **5**. Alcoholysis of intermediate **5** produces **6**, which undergoes an intramolecular Michael addition and elimination to provide tetracyclic intermediate **7**. Finally, ring opening by cleaving the hemiaminal in **7** gives the final product **4**.

Conclusions

In conclusion, an $AlCl_3$-catalyzed synthesis of 3-salicyloylquinoline-4-carboxylic esters from Baylis–Hillman adducts derived from chromones and isatin-derivatives has been developed. This synthetic approach provides a simple, economical, convenient and operationally process for producing biologically active salicyloylquinoline derivatives in good yields. Further research on the reaction mechanism and the application of these salicyloylquinoline derivatives are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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