RSC Advances



View Article Online

View Journal | View Issue

PAPER

Check for updates

Cite this: RSC Adv., 2019, 9, 37057

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

Xuequan Wang, ()** Zhixin Yang, Weihang Miu, Pingting Ye, Mengjiao Bai, Suyue Duan^a and Xianfu Shen^{*b}

A simple and convenient synthesis of 3-salicyloylquinoline-4-carboxylic esters has been developed through an AlCl₃-catalyzed reaction of easily available Baylis–Hillman adducts from chromones and isatinderivatives. 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.

Received 7th October 2019 Accepted 28th October 2019

DOI: 10.1039/c9ra08124k

rsc.li/rsc-advances

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 anticancer,³ anti-tubercular,⁴ anti-plasmodial,⁵ anti-malarial,⁶ antitrypanosomal,⁷ anti-HIV,⁸ anti-inflammatory⁹ and anti-psoriasis¹⁰ 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 coumarin15 and pyrrole.16 Most of these compounds display potent biological properties, including anti-tumor,¹⁷ anti-bacterial,18 photo-antioxidant,19 anti-mitotic and antivascular¹⁴ activities; they could also act as SIRT1 inhibitors¹³ (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 salicyloylquiinclude TMSCl-mediated cyclization of noline 3formylchromone with various anilines²¹ and aromatic nitrogroup 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.

^aKey Laboratory of Natural Pharmaceutical and Chemical Biology of Yunnan Province, School of Science, Honghe University, Mengzi, Yunnan 661100, China. E-mail: huolixuanfeng@126.com

^bCenter for Yunnan-Guizhou Plateau Chemical Functional Materials and Pollution Control, Qujing Normal University, 655011, P. R. China

[†] Electronic supplementary information (ESI) available: Detailed experimental procedures. ¹H NMR and ¹³C NMR spectra for synthesized compounds or other electronic format. See DOI: 10.1039/c9ra08124k



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 isatinderivatives 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 3**a** 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



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

TMSCl, TfOH and HCl afforded trace amounts of the desired product **4a** (Table 1, entry 1–5). To our delight, when AlCl₃ (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 AlCl₃ were investigated (Table 1, entry 7 and 8), and the investigation indicated that the optimal amount of catalyst was AlCl₃ 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-











 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.

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 AlCl₃-catalyzed synthesis of 3salicyloylquinoline-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

This work was supported by the National Natural Science Foundation of China (No. 21602050), Applied Basic Research Project of Yunnan (2017FD154), and Yunnan Province Department of Education Fund (2016ZZX218).

Notes and references

- (a) X. M. Chu, C. Wang, W. Liu, L. L. Liang, K. K. Gong, C. Y. Zhao and K. L. Sun, *Eur. J. Med. Chem.*, 2019, 161, 101; (b) O. Afzal, S. Kumar, M. R. Haider, M. R Ali, R. Kumar, M. Jaggi and S. Bawa, *Eur. J. Med. Chem.*, 2015, 97, 871.
- 2 (a) G. G. Ladani and M. P. Patel, New J. Chem., 2015, 39, 9848;
 (b) P. Sridhar, M. Alagumuthu, S. Arumugam and S. R. Reddy, RSC Adv., 2016, 6, 64460; (c) J. Y. Zhang, S. Wang, Y. Y. Ba and Z. Xu, Eur. J. Med. Chem., 2019, 174, 1.
- 3 (a) W. B. Kuang, R. Z. Huang, Y. L. Fang, G. B. Liang, C. H. Yang, X. L. Ma and Y. Zhang, RSC Adv., 2018, 8, 24376; (b) T. Su, J. C. Zhu, R. Q. Sun, H. H. Zhang, Q. H. Huang, X. D. Zhang, R. L. Du, L. Q. Qiu and R. H. Cao, Eur. J. Med. Chem., 2019, 178, 154; (c) W. T Gao, Z. Y. Li, Q. Q. Xu and Y. Li, RSC Adv., 2018, 8, 38844.
- 4 (a) M. Akula, P. Yogeeswari, D. Sriram, M. Jhac and A. Bhattacharya, *RSC Adv.*, 2016, 6, 46073; (b) B. Tanwar, A. Kumar, P. Yogeeswari, D. Sriram and A. K. Chakraborti, *Bioorg. Med. Chem. Lett.*, 2016, 26, 5960.
- 5 Y. Q. Hu, C. Gao, S. Zhang, L. Xu, Z. Xu, L. S. Feng, X. Wu and F. Zhao, *Eur. J. Med. Chem.*, 2017, **139**, 22.
- 6 (a) S. Vandekerckhove and M. D'hooghe, *Bioorg. Med. Chem.*, 2015, 23, 5098; (b) K. Kaur, M. Jain, R. P. Reddy and R. Jain, *Eur. J. Med. Chem.*, 2010, 45, 3245.
- 7 (a) H. Zhang, J. Collins, R. Nyamwihura, S. Ware, M. Kaiser and I. V. Ogungbe, *Bioorg. Med. Chem. Lett.*, 2018, 28, 1647;
 (b) S. N. Chanquiaa, F. Larreguia, V. Puenteb, C. Labriolac, E. Lombardob and G. G. Liñaresa, *Bioorg. Chem.*, 2019, 83, 526.
- 8 (a) K. C. Sekgota, S. Majumder, M. Isaacs, D. Mnkandhla,
 H. C. Hoppe, S. D. Khanye, F. H. Kriel, J. Coates and
 P. T. Kaye, *Bioorg. Chem.*, 2017, 75, 310; (b) P. Shah,
 D. Naik, N. Jariwala, D. Bhadane, S. Kumar, S. Kulkarni,
 K. K. Bhutani and I. P. Singh, *Bioorg. Chem.*, 2018, 80, 591.
- 9 J. Liu, C. J. Li, L. Ni, J. Z. Yang, L. Li, C. X. Zang, X. Q. Bao, D. Zhang and D. M. Zhang, *RSC Adv.*, 2015, 5, 80553.
- 10 W. J. Zhang, P. H. Lia, M. C. Zhao, Y. H. Gua, C. Z. Dong, H. X. Chen and Z. Y. Du, *Bioorg. Chem.*, 2019, 88, 102899.
- 11 (a) Y. H. Jo, B. Shin, Q. Liu, K. Y. Lee, D. C. Oh, B. Y. Hwang and M. K. Lee, *J. Nat. Prod.*, 2014, 77, 2361; (b) K. Yamanaka, K. S. Ryan, T. A. M. Gulder, C. C. Hughes and B. S. Moore, *J.*

Am. Chem. Soc., 2012, **134**, 12434; (c) X. N. Shi, Y. He, X. Y. Zhang and X. S. Fan, *Org. Chem. Front.*, 2017, **4**, 1967.

- 12 (a) S. M. B. Maezono, T. N. Poudel, L. K. Xia and Y. R. Lee, *RSC Adv.*, 2016, 6, 82321; (b) E. Raj Baral, K. Sharma, M. S. Akhtar and Y. R. Lee, *Org. Biomol. Chem.*, 2016, 14, 10285.
- 13 J. H. Wu, Y. Li, K. X. Chen, H. L. Jiang, M. H. Xu and D. L. Liu, *Eur. J. Med. Chem.*, 2013, **60**, 441.
- 14 H. Y. Lee, C. Y. Chang, M. J. Lai, H. Y. Chuang, C. C. Kuo, C. Y. Chang, J. Y. Chang and J. P. Liou, *Bioorg. Med. Chem. Lett.*, 2015, 23, 4230.
- 15 D. Belkhir-Talbi, M. Makhloufi-Chebli, S. Terrachet-Bouaziz, D. Hikem-Oukacha, N. Ghemmit, L. Ismaili, A. M. S. Silva and M. Hamdi, *J. Mol. Struct.*, 2019, **1179**, 495.
- 16 X. Y. Qi, H. Y. Xiang, Y. H. Yang and C. H. Yang, *RSC Adv.*, 2015, **5**, 98549.
- 17 A. Sood, V. Sharma, A. Chaudhry, R. Kumar, S. Arora, Rajnikant, V. Gupta and M. P. S. Ishar, *Bioorg. Med. Chem. Lett.*, 2014, 24, 4724.
- 18 (a) D. Schillaci, S. Petruso and V. Sciortino, Int. J. Antimicrob. Agents, 2005, 25, 338; (b) A. V. Gadakh, C. Pandit, S. S. Rindhe and B. K. Karale, Bioorg. Med. Chem. Lett., 2010, 20, 5572; (c) M. V. Raimondi, R. Listro, M. G. Cusimano, M. L. Franca, T. Faddetta, G. Gallo, D. Schillaci, S. Collina, A. Leonchiks and G. Barone, Bioorg. Med. Chem., 2019, 27, 721.
- 19 Y. Dobashi, J. I. Kondou and Y. Ohkatsu, *Polym. Degrad. Stab.*, 2005, **89**, 140.
- 20 (a) M. L. N. Rao and B. S. Ramakrishna, Eur. J. Org. Chem., 2017, 2017, 5080; (b) A. S. Plaskon, S. V. Ryabukhin, D. M. Volochnyuk, A. N. Shivanyuk and A. A. Tolmachev, Tetrahedron, 2008, 64, 5933; (c) V. O. Iaroshenko, S. Mkrtchyan, G. Ghazaryan, A. Hakobyan, A. Maalik, L. Supe, A. Villinger, A. Tolmachev, D. Ostrovskyi, V. Y. Sosnovskikh, T. V. Ghochikyan and P. Langer, Synthesis, 2011, 469.
- 21 (a) A. S. Plaskon, S. V. Ryabukhin, D. M. Volochnyuk,
 K. S. Gavrilenko, A. N. Shivanyuk and A. A. Tolmachev, J. Org. Chem., 2008, 73, 6010; (b) S. V. Ryabukhin,
 A. S. Plaskon, D. M. Volochnyuk and A. A. Tolmachev, Synthesis, 2007, 1861.
- 22 D. Basavaiah, R. J. Reddy and J. S. Rao, *Tetrahedron Lett.*, 2006, **47**, 73.
- 23 (a) K. K. Dong and Q. Huang, *Tetrahedron Lett.*, 2019, 60, 1871; (b) T. Z. Dai, Q. Y. Li, X. F. Zhang and C. H. Yang, *J. Org. Chem.*, 2019, 84, 5913.
- 24 (a) S. Z. Luo, X. L. Mi, H. Xu, P. G. Wang and J. P. Cheng, J. Org. Chem., 2004, 69, 8413; (b) D. Basavaiah and A. J. Rao, Tetrahedron Lett., 2003, 44, 4365.
- 25 P. Zhou, B. Hu, S. Y. Zhao, Q. H. Zhang, Y. Q. Wang, X. Li and F. C. Yu, *Tetrahedron Lett.*, 2018, **59**, 3116.