ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 9887

Received 9th June 2014,
Accepted 3rd July 2014

DOI: 10.1039/c4cc04377d

www.rsc.org/chemcomm

Base-promoted synthesis of coumarins from salicylaldehydes and aryl-substituted 1,1-dibromo-1-alkenes under transition-metal-free conditions†

Jianming Liu,*[a] Xin Zhang,[a] Lijun Shi,[b] Muwen Liu,[a] Yuanyuan Yue,[a] Fuwei Li*[b] and Kelei Zhuo*[a]

Facile synthesis of coumarin *via* the tandem reaction of salicylaldehyde with aryl-substituted 1,1-dibromo-1-alkene was developed. This new protocol proceeds smoothly under mild and transition-metal-free conditions, it allows rapid access to coumarins containing various heteroatoms that are more difficult to prepare by traditional methods. Based on the isolated intermediate of 4-(diethylamino)-3-phenylchroman-2-one and detailed mechanistic studies, a credible tandem pathway was proposed.

The coumarin scaffold has been found in many natural products and pharmaceuticals, and it has also been considered as a valuable synthetic building block in material sciences.[1–3] 3-Arylcoumarins are mainly prepared by the following five strategies: (a) the earliest condensation of salicylaldehyde with phenylacetic acid or arylacetonitrile;[4] (b) Pd-catalysed cross coupling of simple coumarin with aryl halide or arylboronic acid;[5,6] (c) Pd-catalysed carbonylative annulation;[7] (d) base promoted three-component coupling using arynes, malonates and DMF;[8] and (e) the oxidative hydrolysis of 3-phenylspiro[chroman-2,2′-[1,3]dithiane].[9] Although these methods exhibited their individual advantages, they generally involved multistep procedures, sometimes harsh reaction conditions, preparation of special starting materials, the combination with strong bases, the difficult synthesis of coumarins containing various heteroatoms, and the requirement of transition metal complexes.[10] To avoid the drawbacks of the above processes, such as toxicity and noble transition metal remaining in final products as a trace impurity, transition-metal-free cross coupling reactions should be appreciated.[11,12] Therefore, developing a new synthetic route that is not dependent on precious metals or ligands would be ideal in terms of cost and simplicity.

Recently, the tandem reactions of aryl-substituted 1,1-dibromo-1-alkenes have emerged as powerful and versatile synthetic intermediates.[13,14] 1,1-Dibromo-1-alkenes, owing to their high regioselectivity and easy accessibility from available starting materials, have been exploited, notably as key units for the construction of various heterocycles and carbocycles.[15–18] Herein, we report a general and facile procedure for the preparation of coumarins by the base-promoted tandem reaction of 1,1-dibromo-1-alkene with salicylaldehyde derivatives. This development is based on the retrosynthetic analysis depicted in Scheme 1. 3-Arylcoumarins should be prepared by base-promoted intramolecular cyclization of aryl-substituted 1,1-dibro-1-alkenes, which act as synthetic equivalents to the phenylacetyl compounds (Scheme 1). We envisaged that aryl-substituted 1,1-dibromo-1-alkenes were possibly suitable synthetic equivalents to the phenylacetyl synthons, since they could act as C–O cross coupling acceptors and then the bromine group was attacked by OH^-. Lastly, the desired product was prepared by elimination. In this context, we now developed a new base-promoted protocol for the intramolecular cyclization of salicylaldehydes and aryl-substituted 1,1-dibromo-1-alkenes to generate substituted coumarins. This method is not only a new route for coumarin synthesis but also a new type of base-promoted tandem reaction.

Our evaluation started with the reaction of salicylaldehyde (**1a**) and (2,2-dibromovinyl)benzene (**2a**) in the presence of base under an air atmosphere in DMF at 110 °C (Table S1, see ESI†). Although only a trace yield of the desired **3a** was obtained with Na_2CO_3 as the promoter, it could initiate such a transformation

Scheme 1 Retrosynthetic analysis of coumarins.

[a] *Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: jmliu@htu.cn, klzhuo@263.net*

[b] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China. E-mail: fuweili@licp.cas.cn*

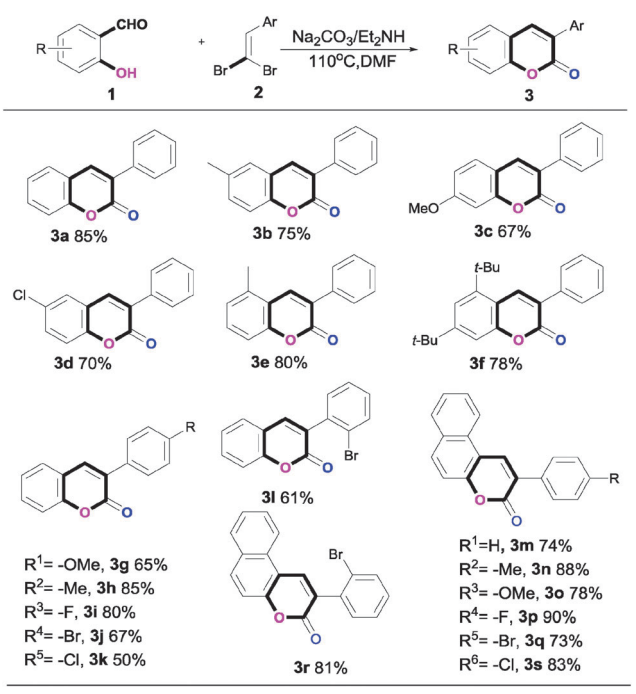
† Electronic supplementary information (ESI) available. CCDC 947235. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc04377d

(Table S1, ESI,† entry 1). Surprisingly, a perfect 85% yield was realized only by the addition of Et_2NH into the above system (Table S1, ESI,† entry 2). However, Et_2NH alone gave no reaction (Table S1, ESI,† entry 3). These obvious differences indicated that the synergetic function of inorganic Na_2CO_3 and organic Et_2NH led to such an efficient conversion. Among the screened inorganic bases (Table S1, ESI,† entries 4–8), Na_2CO_3 was the most efficient base. The trace yield of the desired product was observed when DMAc, toluene and 1,4-dioxane were used as solvents (Table S1, ESI,† entries 9–11). NMP was also an effective solvent, and promoted smoothly the reaction in 84% yield (Table S1, ESI,† entry 12). The decrease and increase of the temperature resulted in relatively low yield of the desired product (Table S1, ESI,† entries 13 and 14).

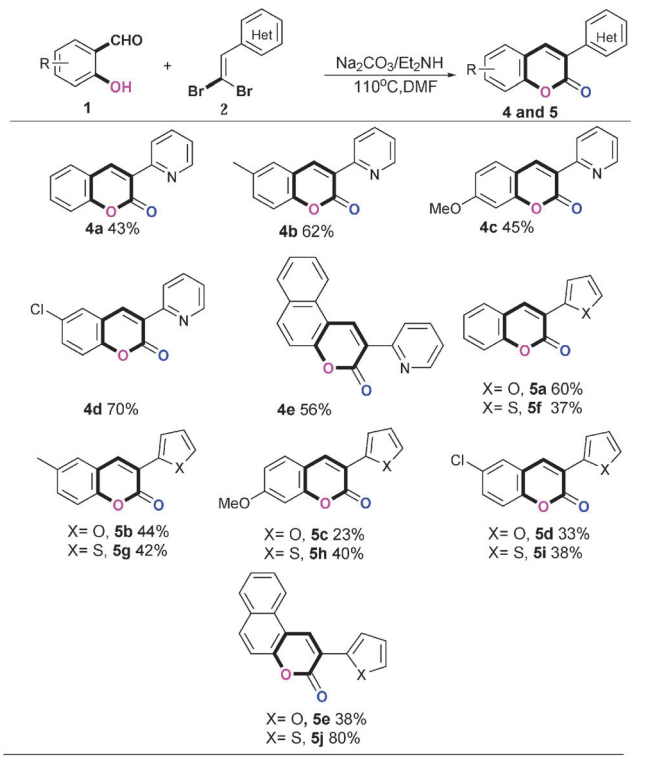
With the optimized conditions in hand, we started to investigate other substrates in base-promoted tandem reaction. First of all, various salicylaldehydes were employed to construct the coumarins with (2,2-dibromovinyl)benzenes (Scheme 2). For salicylaldehydes, a series of functional groups on the phenyl ring (*e.g.*, methyl, methoxyl, chloro, and tertiary butyl) were compatible with the present catalytic system, and the desired products were isolated in excellent yields (**3a–3f**). This indicates that the present reaction has good functional-group tolerance. To our delight, both the *o*-methyl and *o*-*t*-butyl substituted salicylaldehydes were similarly found to be suitable substrates for this transformation and gave the desired products in 80% and 78% yields, respectively. Furthermore, various functional groups can be tolerated in 1,1-dibromo-1-alkenes with a phenyl fragment, including a large range of methoxyl, methyl, fluoro, halo and brine substituents. It was found that both electron-withdrawing groups and electron-donating groups at the *para* position of 1,1-dibromo-1-alkenes gave the desired products in good yield from 50% to 85% (**3g–3l**). The structure of **3h** was unambiguously confirmed by single-crystal X-ray diffraction analysis (see ESI†). Meanwhile, the tandem reaction of 2-hydroxy-1-naphyadehyde and 1,1-dibromo-1-alkenes with various electron-rich and electron-poor groups also provided the substituted coumarins in good yields under the optimized reaction conditions (**3m–3s**). In all, the ability to incorporate the different substituents makes this reaction more attractive for increasing the coumarin complexity.

Encouraged by these promising results, we further applied these base-promoted tandem reaction conditions to construct a variety of important nitrogen- and sulfur-containing heterocyclic compounds (Scheme 3). To our delight, 1,1-dibromo-1-alkenes with an *ortho*-substituent on the pyridine ring were selectively treated with salicylaldehydes, affording the corresponding products in 45% to 70% yields (**4a–4e**). Similarly, 2-(2,2-dibromovinyl)furans were coupled with salicylaldehydes to produce the substituted coumarins in moderate yields (**5a–5e**). Lastly, various salicylaldehydes were also shown to couple with 2-(2,2-dibromovinyl)thiophenes in moderate to good yields (**5f–5j**).

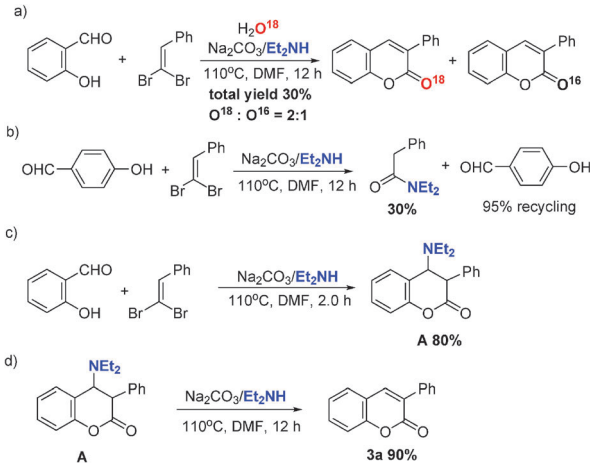
To explore the mechanism for this reaction, control experiments were carried out under the standard reaction conditions (Scheme 4). Firstly, radical trapping experiments were also conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to elucidate whether the reaction involves radical species.



Scheme 2 Base-promoted tandem reactions of salicylaldehydes with 1,1-dibromoalkenes. Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), Na_2CO_3 (2.0 mmol), and Et_2NH (0.50 mL) in DMF (5.0 mL) at 110 °C for 12 h in air. Isolated yields.



Scheme 3 Base-promoted tandem reactions of salicylaldehydes with other challenging substrates. Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), Na_2CO_3 (2.0 mmol), and Et_2NH (0.50 mL) in DMF (5.0 mL) at 110 °C for 12 h in air. Isolated yields.



Scheme 4 Preliminary mechanistic study.

The result showed that no radical species were involved in the tandem reaction (see ESI† for details). Furthermore, the reaction between **1a** and **2a** in the presence of H_2O^{18} afforded the ^{18}O-labeled product **3a** in 20% yield (Scheme 4a), demonstrating that the carbonyl oxygen atom of coumarin originated from H_2O produced by the reaction as our initial assumption. When 4-hydroxybenzaldehyde was subjected to be employed under the optimized reaction conditions, *N*,*N*-diethyl-2-phenylacetamide was obtained in 30% yield (Scheme 4b), thus demonstrating that the aldehyde group was essential for the tandem reaction. At an early stage (2.0 h) of the reaction of **1a** with **2a** in DMF under standard conditions, a large amount (80%) of intermediate (4-(diethylamino)-3-phenylchroman-2-one) was expectedly detected along with **3a** by LC-MS analysis of the reaction mixture. Once formed, the intermediate was converted into the desired product during the progress of the reaction. Fortunately, 4-(diethylamino)-3-phenylchroman-2-one could be isolated from the mixture, and the structure was unambiguously confirmed by NMR and LC-MS (Scheme 4c). The treatment of **A** under standard conditions gave **3a** in 90% yield (Scheme 4d). These results indicated that the present reaction proceeded directly involving the formation of intermediate **A**.

A possible mechanism for the synthesis of coumarins is proposed in Fig. 1. According to the above obtained results and the previous reports,[8] salicylaldehyde would undergo the interaction with 1,1-dibromo-1-alkene to generate the key intermediate **I**. The next step is believed to be accomplished through the elimination of Br^-. Then the nucleophile OH^- attacked intermediate **II**

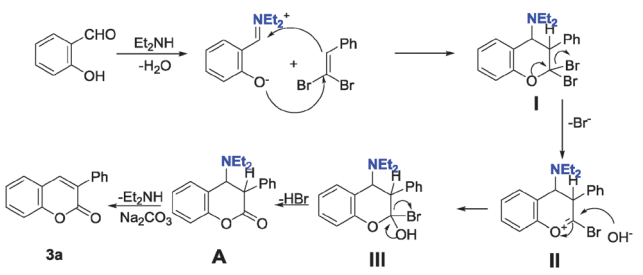


Fig. 1 Proposed reaction mechanism.

to give intermediate **III**. In the presence of base, intermediate **III** eliminated HBr to generate intermediate **A**. Finally, intermediate **A** could undergo the elimination of Et_2NH by the driving force of aromatization to form the target product **3a**.

In conclusion, we have demonstrated for the first time the base-promoted cascade reaction of 1,1-dibromo-1-alkenes with salicylaldehydes under mild conditions. Several substituted salicylaldehydes and various aryl-substituted 1,1-dibromo-1-alkenes were found to be suitable substrates for the tandem reaction. This work opens up a new approach for the construction of heteroaromatic coumarins from available starting materials which show promising potential in biological activities and pharmaceutical applications. Based on the isolated intermediate of 4-(diethylamino)-3-phenylchroman-2-one and detailed mechanistic studies, a credible tandem pathway was proposed.

We are grateful for financial support from National Natural Science Foundation of China (21103044, 21173070, and 21205029), Project funded by China Postdoctoral Science Foundation, and Plan for Scientific Innovation Talent of Henan Province (No. 124200510014).

Notes and references

1 (*a*) P. Wan, B. Barker, L. Diao, M. Fischer, Y. Shi and C. Yang, *Can. J. Chem.*, 1996, **74**, 465; (*b*) R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367.
2 T. Rosenau, A. Potthast, T. Elder and P. Kosma, *Org. Lett.*, 2002, **4**, 4285.
3 S. R. Angle, J. D. Rainier and C. Woytowicz, *J. Org. Chem.*, 1997, **62**, 5884.
4 (*a*) D. Viña, M. J. Matos, M. Yáñez, L. Santanab and E. Uriarteb, *Med. Chem. Commun.*, 2012, **3**, 213; (*b*) K. V. Sashidhara, G. R. Palnati, S. R. Avula and A. Kumar, *Synlett*, 2012, 611; (*c*) L. M. Kabeya, A. A. de Marchi, A. Kanashiro, N. P. Lopes, C. H. T. P. da Silva, M. T. Pupob and Y. M. Lucisano-Valima, *Bioorg. Med. Chem.*, 2007, **15**, 1516; (*d*) C. Mhiri, F. Ladhar, R. El Gharbi and Y. Le Bigot, *Synth. Commun.*, 1999, **29**, 1451.
5 (*a*) M. S. Schiedel, C. A. Briehn and P. Bäuerle, *Angew. Chem., Int. Ed.*, 2001, **41**, 4677; (*b*) M. J. Matos, S. Vazquez-Rodriguez, F. Borges, L. Santana and E. Uriarte, *Tetrahedron Lett.*, 2011, **52**, 1225.
6 (*a*) A. Unsinn, S. H. Wunderlich and P. Knochela, *Adv. Synth. Catal.*, 2013, **355**, 989; (*b*) M. Min, B. Kim and S. Hong, *Org. Biomol. Chem.*, 2012, **10**, 2692; (*c*) S. Martins, P. S. Branco, M. C. de la Torre, M. A. Sierra and A. Pereira, *Synlett*, 2010, 2918.
7 (*a*) D. V. Kadnikov and R. C. Larock, *Org. Lett.*, 2000, **2**, 3643; (*b*) D. V. Kadnikov and R. C. Larock, *J. Organomet. Chem.*, 2003, **687**, 425; (*c*) J. Ferguson, F. Zeng and H. Alper, *Org. Lett.*, 2012, **14**, 5602; (*d*) X.-F. Wu, L. Wu, R. Jackstell, H. Neumann and M. Beller, *Chem. – Eur. J.*, 2013, **19**, 12245.
8 H. Yoshida, Y. Ito and J. Ohshita, *Chem. Commun.*, 2011, **47**, 8512.
9 J.-W. Lee and B. List, *J. Am. Chem. Soc.*, 2012, **134**, 18245.
10 (*a*) M. Min, Y. Kim and S. Hong, *Chem. Commun.*, 2013, **49**, 196; (*b*) Y. M. Li, Z. S. Qi, H. F. Wang, X. M. Fu and C. Y. Duan, *J. Org. Chem.*, 2012, **77**, 2053; (*c*) G. Blay, M. C. Muñz, J. R. Pedro and A. Sanz-Marco, *Adv. Synth. Catal.*, 2013, **355**, 1071; (*d*) G. Battistuzzi, S. Cacchi, I. D. Salve, G. Fabrizi and L. M. Parisi, *Adv. Synth. Catal.*, 2005, **347**, 308; (*e*) Z. Y. Tang and Q. S. Hu, *Adv. Synth. Catal.*, 2004, **346**, 1635; (*f*) F. Fontana, F. Minisci, M. C. Nogueira Barbosa and E. Vismara, *J. Org. Chem.*, 1991, **56**, 2866.
11 (*a*) I. Thomé, C. Besson, T. Kleine and C. Bolm, *Angew. Chem., Int. Ed.*, 2013, **52**, 7509; (*b*) W. Chen, Y. C. Zhang, L. Zhang, M. Wang and L. Wang, *Chem. Commun.*, 2011, **47**, 10476.
12 (*a*) E. Shirakawa, K.-I. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537; (*b*) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, **2**, 1044; (*c*) W. Liu, H. Cao, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737.

13 (*a*) M. Okutani and Y. Mori, *J. Org. Chem.*, 2009, **74**, 442; (*b*) Z.-J. Wang, F. Yang, X. Lv and W. L. Bao, *J. Org. Chem.*, 2011, **76**, 967; (*c*) Z. W. Chen, H. F. Jiang, Y. B. Li and C. R. Qi, *Chem. Commun.*, 2010, **46**, 8049; (*d*) X. Zhu, A. J. Lin, Y. Shi, J. Y. Guo, C. J. Zhu and Y. X. Cheng, *Org. Lett.*, 2011, **13**, 4382.

14 (*a*) M. L. N. Rao, D. N. Jadhav and P. Dasgupta, *Org. Lett.*, 2010, **12**, 2048; (*b*) G. Chelucci, F. Capitta and S. Baldino, *Tetrahedron*, 2008, **64**, 10250; (*c*) K. M. Tao, J. L. Zheng, Z. G. Liu, W. Shen and J. C. Zhang, *Tetrahedron Lett.*, 2010, **51**, 3246; (*d*) W. Shen and S. A. Thomas, *Org. Lett.*, 2000, **2**, 2857.

15 (*a*) C. S. Bryan and M. Lautens, *Org. Lett.*, 2010, **12**, 2754; (*b*) C. S. Bryan, J. A. Braunger and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 7064.

16 (*a*) G. Chelucci, *Chem. Rev.*, 2012, **112**, 1344; (*b*) W. Zhang, W. Li and C. Kuang, *Prog. Chem.*, 2013, **25**, 1149; (*c*) A. Coste, F. Couty and G. Evano, *Org. Lett.*, 2009, **11**, 4454; (*d*) H. Xu, Y. Zhang, J. Q. Huang and W. Z. Chen, *Org. Lett.*, 2010, **12**, 3704; (*e*) B. P. Berciano, S. Lebrequier, F. Besselièvre and S. G. Piguel, *Org. Lett.*, 2010, **12**, 4038; (*f*) K. Jouvin, Al. Bayle, F. Legrand and G. Evano, *Org. Lett.*, 2012, **14**, 1652.

17 (*a*) M. Lera and C. J. Hayes, *Org. Lett.*, 2000, **2**, 3873; (*b*) W. Shen and A. Kunzer, *Org. Lett.*, 2002, **4**, 1315; (*c*) H. Xu, S. J. Gu, W. Z. Chen, D. C. Li and J. M. Dou, *J. Org. Chem.*, 2011, **76**, 2448; (*d*) Z. Huang, R. Shang, Z.-R. Zhang, X.-D. Tan, X. Xiao and Y. Fu, *J. Org. Chem.*, 2013, **78**, 4551; (*e*) L. Liu, Y. L. Wang, Z. P. Zeng, P. X. Xu, Y. X. Gao, Y. W. Yin and Y. F. Zhao, *Adv. Synth. Catal.*, 2013, **355**, 659.

18 (*a*) R. Riveiros, L. Saya, J. P. Sestelo and L. A. Sarandeses, *Eur. J. Org. Chem.*, 2008, 1959; (*b*) M. Arthuls, R. Pontikis and J. C. Florent, *Org. Lett.*, 2009, **11**, 4608; (*c*) C. Y. Sun and B. Xu, *J. Org. Chem.*, 2008, **73**, 7361; (*d*) Y. Fukudome, H. Naito, T. Hata and H. Urabe, *J. Am. Chem. Soc.*, 2008, **130**, 1820; (*e*) A. M. Zhang, X. L. Zheng, J. F. Fan and W. Shen, *Tetrahedron Lett.*, 2010, **51**, 828; (*f*) J. M. Liu, N. F. Zhang, Y. Y. Yue, D. Wang, Y. L. Zhang, X. Zhang and K. L. Zhuo, *RSC Adv.*, 2013, **3**, 3865.

