Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

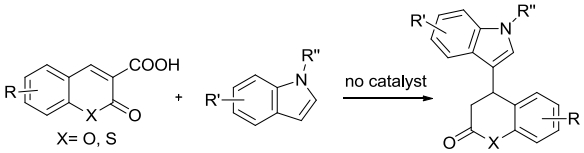
Catalyst-free tandem Michael addition/decarboxylation of (thio)coumarin-3-carboxylic acids with indoles: facile synthesis of indole-3-substituted 3,4-dihydro(thio)coumarins

Zhuzhou Shao, Lubin Xu, Liang Wang, Hongtao Wei and Jian Xiao*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The tandem Michael addition/decarboxylation of (thio)coumarin-3-carboxylic acids with indoles has been developed and the biologically important indole-3-substituted dihydrocoumarins were obtained in good to excellent yields under catalyst-free conditions.

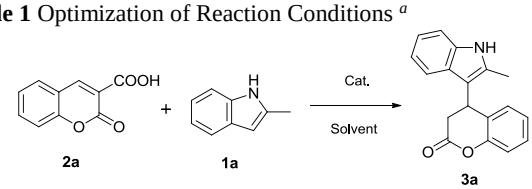
Both indoles[1] and 3, 4-dihydrocoumarins[2] are the privileged structures of a large number of heterocyclic compounds in nature. The derivatives of the compounds of these two families exhibit a broad spectrum of biological and pharmacological properties,[3,4] which exist in numerous drugs and biologically active natural products. Due to the high significance of these two classes of compounds in drug discovery, the synthesis of the compounds containing both of these two moieties is highly desirable. However, up to now**,** only few methods are available for the synthesis of indole-3-substituted dihydrocoumarins. In 2006, Tang *et al* reported a $Mg(OTf)_2$ catalyzed tandem reaction involving consecutive Michael additions between indoles, 3-nitrocoumarins and methyl vinyl ketones which gave rise to multi-functionalized 3,4-dihydrocoumarins.[5] Recently, Mattson disclosed conjugate addition of indole**s** to coumarins using urea palladacycles as a hybrid catalyst to prepare this motif.[6] Besides conjugate addition, multicomponent reaction can also be employed to produce indole-3-substituted dihydrocoumarins. Srivastava *et al* reported a saccharin-based functional ionic liquid mediated multicomponent reaction involving Knoevenagel condensation and Michael addition to yield the indole-3-substituted dihydrocoumarins efficiently.[7] Despite the above protocols to prepare indole-3-substituted dihydrocoumarins, there are still drawbacks such as the lack of substrate generality and use of expensive catalyst and reagents. Thus the avoidance of use of precious catalyst and materials is highly desirable for organic chemists. During our great interest in manipulation of coumarin derivatives, we have developed a facile catalyst-free tandem addition/decarboxylation of 2-alkylazaarenes with (thio)coumarin-3-carboxylic acids via sp^3 C-H activation for efficient construction of azaarenes substituted 3, 4-dihydro(thio)coumarins.[8a] As a continuation of this work and development of efficient and green manner to construct biologically active molecules,[8] herein we present a facile catalyst-free tandem Michael addition/decarboxylation reaction to construct indole-3-substituted dihydrocoumarins in one step from simple and readily available indoles and coumarin-3-carboxylic acids (Scheme 1).



Scheme 1 Tandem Michael addition/decarboxylation of indoles with (thio)coumarin-3-carboxylic acids.

Our initial study commenced with the conjugate addition of 2-methylindole **1a** with coumarin-3-carboxylic acid **2a** in the presence of 10 mol% $Sc(OTf)_3$ (Table 1, entry 1). To our delight, the decarboxylative product **3a** was obtained in dioxane at 120°C in high yield (96%). However, if CH_3CO_2H (10 mol%) was exploited as catalyst, product **3a** was afforded only in very low yield (Table 1, entry 2). The most intriguing result was that when this reaction was conducted under catalyst-free condition, the desired product **3a** could be obtained in excellent yield (98%) after isolation (Table 1, entry 3), which was superior to that using Lewis acids or Brønsted acids as catalysts. The employment of other solvents, e.g. THF, DMF, CF_3CH_2OH, DCE and toluene, led to inferior yields (Table 1, entries 4-9), which demonstrated that the option of solvent was critical this reaction. Furthermore, the lower temperature was detrimental to the yield of the transformation (Table 1, entries 10-11). With the optimized

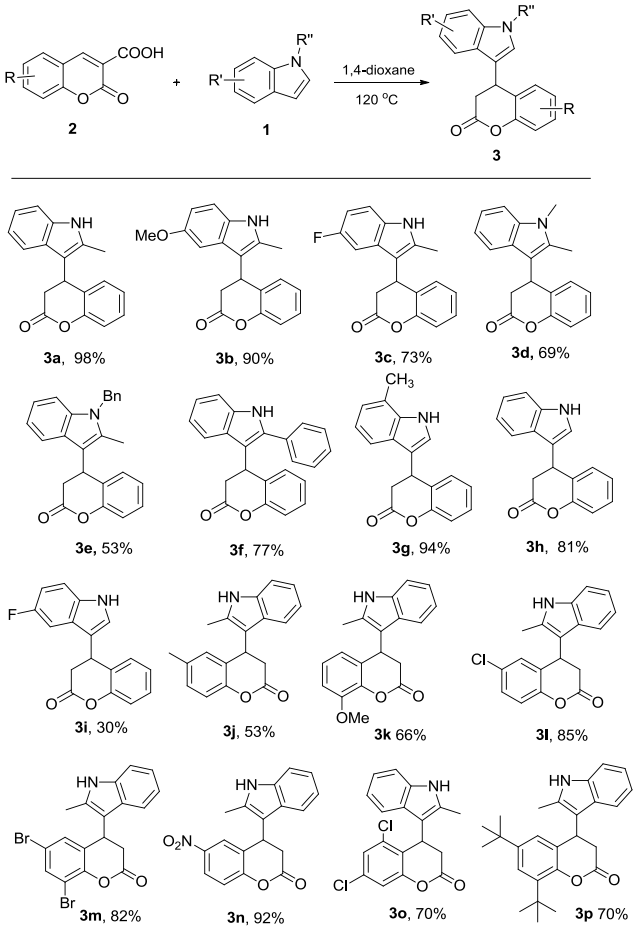
Table 1 Optimization of Reaction Conditions [a]



Entry	Cat.	Solvent	Temp.(°C)	Yield(%)[b]
1	$Sc(OTf)_3$	dioxane	120	96
2	CH_3COOH	dioxane	120	24
3	-	dioxane	120	98
4	-	THF	120	87
5	-	DMSO	120	0
6	-	DMF	120	59
7	-	CF_3CH_2OH	120	52
8	-	DCE	120	56
9	-	toluene	120	64
10	-	dioxane	100	75
11	-	dioxane	80	72

[a] Reactions were conducted with **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (10 mol%) in 1 mL solvent for 48 h. [b] Isolated yield.

Scheme 2 Substrate scope of indoles and coumarin-3-carboxylic acids [a,b]

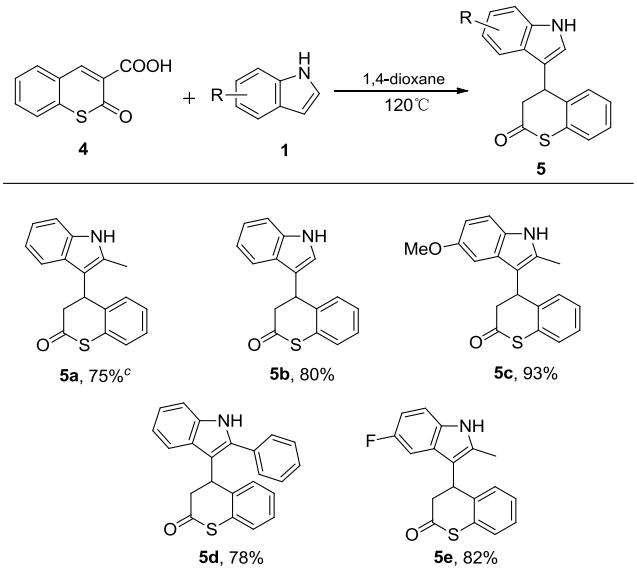


[a] Reactions were conducted with indoles **1** (0.75 mmol), coumarin-3-carbpxylic acid **2** (0.3 mmol) in 2 mL dioxane at 120°C for 48 h. [b] The yields indicated are the isolated yield by column chromatography.

conditions in hand, the scope of indoles was investigated and the results are given in Scheme 2. A series of indoles reacted with **2a** under the optimized condition to produce the corresponding products **3b**-**3i** in modest to excellent yields. Notably, the substituents in the phenyl ring of indole have a significant influence on the reactivity. The electron donating group still gave the desired product in excellent yields (Scheme 2, **3b**). Conversely, an electron-withdrawing substituent such as fluorine will decrease the nucleophilicity of C3 of indole, thus affording lower yield (Scheme 2, **3c, 3i**). When the *N*-methyl and *N*-benzyl protected 2-methylindoles were exploited as substrates, the analogous products were generated in moderate yields (**3d**, 69% and **3e**, 53%). The bulky 2-phenyl indole and 7-methyl indole are also tolerated (Scheme 2, **3f**, **3g**). Indole gave lower yield compared to the electron rich 2-methyl indole and 7- methyl indole (Scheme 2, **3h**). Subsequently, a variety of coumarin-3-carboxylic acids were examined (Scheme 2, **3j**-**3p**). Different from substrate **1**, the substrates **2** with electron-donating groups gave inferior results and electron-withdrawing groups gave better results (Scheme 2, **3j**-**3p**) It can be rationalized that the electron-withdrawing groups such as Cl, Br and NO_2 in phenyl ring of coumarin-3-carboxylic acids can increase the electrophilicity of the alkene to facilitate the conjugate addition effectively. Interestingly, when C6, C8-positions of phenyl ring were substituted with two bulky *tert*-butyl groups, the corresponding product **3p** could still be isolated in good yield (70%).

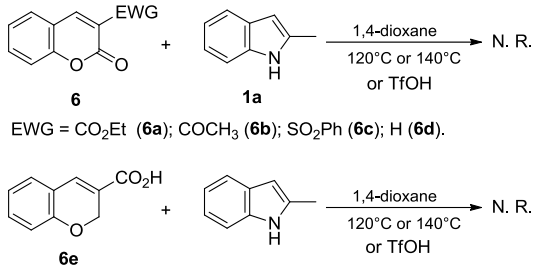
Encouraged by the success of coumarins-3-carboxylic acid, we extended the substrate scope to thiocoumarin-3-carboxylic acid since thiocoumarin derivatives also exhibit a broad spectrum of pharmacological properties.[9,10] Gratifyingly, when thiocoumarin-3-carboxylic acid **4** was allowed to react with indoles **1**, the corresponding indole-3-substituted 3, 4-dihydrothiocoumarins **5** could be isolated in good to excellent yield (Scheme 3).

Scheme 3 Reaction of thiocoumarin-3-carboxylic acids with indoles [a,b]



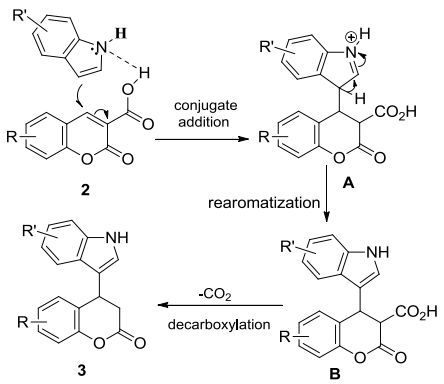
[a] Reactions were conducted with indoles **1** (0.75 mmol), thiocoumarin-3-carbpxylic acid **4** (0.3 mmol) in 2 mL dioxane at 120 °C for 48 h. [b] The yields indicated are the isolated yield by column chromatography. [c] Reation time was 30 h.

To elucidate the reaction mechanism, control experiments were carried out with ethyl coumarin-3-carboxylate **6a**, 3-acetyl coumarin **6b**, coumarin-3-phenylsulfone **6c**, coumarin **6d** and 2H-chromene-3-carboxylic acid **6e** under the standard condition. Remarkably, no reaction occurred and all the substrates remained intact even in the presence of TfOH catalyst or the reaction temperature was raised to 140 °C. Thus it can be concluded that the carboxyl group in C-3 position of coumarin was indispensable for the success of this reaction.[11] The failure of the reaction of 2H-chromene-3-carboxylic acid **6e** might be rationalized that without synergistic activation of alkene by carboxylic group and lactone moiety, Michael acceptor is not electrophilic enough for the conjugate addition.



Scheme 4 Control experiments

According to the experimental results, a possible mechanism was proposed as follows: the alkene of coumarin-3-carboxylic acid is rendered electrophilic synergistically by carboxylic group and lactone moiety, while hydrogen bond formation between nitrogen atom and hydroxyl group not only render alkene more electrophilic but also bring the indole close to electron deficient double bond for subsequent conjugate addition to afford intermediate **A**. A subsequent rearomatization followed by decarboxylation furnishes the product **3**.



Scheme 5 Proposed mechanism.

Conclusions

In summary, we present a facile catalyst-free tandem Michael addition/decarboxylation of indoles with (thio)coumarin-3-carboxylic acids for the efficient construction of indole-3-substituted 3,4-dihydro(thio)coumarins. A broad scope of coumarins, thiocoumarins and indoles has been defined and the coupled products were isolated in good to excellent yields. This tandem reaction provides an efficient and novel protocol to construct this biologically important architecture without catalyst in one step.

Acknowledgement. We are grateful to the National Natural Science Foundation of China (No. 21102142) and the Outstanding Young Scientist Award Foundation of Shandong Province (No. BS2011YY007, BS2013YY002). Financial supports from Talents of High Level Scientific Research Foundation (No. 631223) of Qingdao Agricultural University is also gratefully acknowledged.

. Notes and references

College of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao, 266109, China.
E-mail:chemjxiao@gmail.com, chemjianxiao@gmail.com

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1. For exemples, see: (a) R. J. Sundberg, *Indoles*; Academic: New York, 1996; (b) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278; (c) T. Kawasaki and K. Huguchi, *Nat. Prod. Rep.*, 2005, **22**, 761; (d) S. E. O'Connor and J. J. Maresh, *Nat. Prod. Rep.*, 2006, **23**, 532; (e) K. Huguchi and T. Kawasaki, *Nat. Prod. Rep.*, 2007, **24**, 843.
2. For exemples, see: (a) R. D. H. Murray, *Nat. Prod. Rep*., 1989, **6**, 591; (b) R. D. H. Murray, *Nat. Prod. Rep.*,1995, **12**, 477; (c) A. Estevez-Braun, A. G. Gonzalez, *Nat. Prod. Rep.*, 1997, **14**, 464; (d) G. P. McGlacken, I. J. S. Fairlamb, *Nat. Prod. Rep*., 2005, **22**, 369; (e) F. Asai, M. Iinuma, T. Tanaka, M. Mizuno, *Phytochemistry*, 1991, **30**, 3091; (f) F. Asai, M. Iinuma, T. Tanaka, M. Mizuno, *Heterocycles*, 1992, **33**, 229; (g) F. Asai, M. Iinuma, T. Tanaka, M. Mizuno, *Phytochemistry*, 1992, **31**, 2487.
3. For indoles substituted at C3 position, see examples: (a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M.Freidinger,W. L.Whitter, G. F. Lundell, D. F. Veber and P. S. Anderson, *J.Med. Chem*., 1988, **31**, 2235; (b) D. A. Horton, G. T. Bourne andM. L. Smythe, *Chem. Rev*., 2003, **103**, 893. (c) M. Gompel, M. Leost, E. B. D. Joffe, L. Puricelli, L. H. Franco, J.Palermo and L. Meijer, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1703; (d) M. A. A. Radwan and M. El-Sherbiny, *Bioorg. Med. Chem*., 2007, **14**, 1206. (e) S. Takahashi, T. Mathsunase, C. Hasegawa, H. Saito, D. Fujita, F. Kiwchi and Y. Tsuda, *Chem. Pharm. Bull*., 1998, **46**, 1527. (f) S. R. Naik, J. Harindran and A. B. Varde, *J. Biotechnol*., 2001, **88**, 1. (g) G. R. Pettit, J. C.Knight,D. L. Herald,R. Davenport,R.K. Pettit, B. E. Tucker and J. M. Schmidt, *J. Nat. Prod*., 2002, **65**, 1793. (h) A. Nishida, M. Fuwa, Y. Fujikawa, E. Nakahata, A. Furuno and M. Nakagawa, *Tetrahedron Lett*., 1998, **39**, 5983. (i) G. Guella, I. Mancini, I. N'Diaye and F. Pietra, *Helv. Chim. Acta*, 1994, **77**, 1999; (j) I. N'Diaye, G. Guella, I. Mancini and F. Pietra, *Tetrahedron Lett.*, 1996, **37**, 3049.
4. For 3,4-dihydrocoumarins, see examples: (a) F. Roelens, K. Huvaere, W. Dhooge, M. Van Cleemput, F. Comhaire, D. De Keukeleire, *Eur. J. Med. Chem*. 2005, **40**, 1042. (b) A. Kumar, B. K. Singh, R. Tyagi, S. K. Jain, S. K. Sharma, A. K. Prasad, H. G. Raj, R. C. Rastogi, A. C. Watterson, V. S. Parmar, *Bioorg. Med. Chem*. 2005, **13**, 4300. (f) J. Modranka, A. Albrecht, R. Jakubowski, H. Krawczyk, M. Rozalski, U. Krajewska, A. Janecka, A. Wyrebska, B. Rozalska, T. Janecki, *Bioorg. Med. Chem*. 2012, **20**, 5017. (g) J. Yang, G. Y. Liu, F. Dai, X. Y. Cao, Y. Kang, L. M. Hu, J. J. Tang, X. Z. Li, X. L. Jin, B. Zhou, *Bioorg. Med. Chem. Lett*. 2011, **21**, 6420. (h) E. Tyrrell, K. Mazloumi, D. Banti, P. Sajdak, A. Sinclair, A. Le Gresley, *Tetrahedron Lett*. 2012, **53**, 4280. 1.
5. Y. Tang, M.-C. Ye, Y. Y. Yang, X.-L. Sun, Z. Ma, W. M. Qin, *Synlett*, **2006**, 1240.
6. D. M. Nickerson, A. E. Mattson, *Chem. Eur. J*., 2012, **18**, 8310.
7. A. Kumar, P. Kumar, V. D. Tripathi,S Srivastava, *RSC Advances*, 2012, **2**, 11641.
8. (a) Xu, L.; Shao, Z.; Wei, H.; Wang, L.; Xiao, J.; *Org. Lett*., 2014, in press, doi: 10.1021/ol403541g; (b) Xiao, J. Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.*, 2012, **14**, 676; (c) J. Xiao, *Org. Lett*., 2012, **14**, 1716; (d) T. Liang, J. Xiao, Z. Y. Xiong, X. Li, *J. Org. Chem*,. 2012, **77**, 3583; (e) J. Xiao, K. Zhao, T. P. Loh, *Chem. Comm.*, 2012, **48**, 3548.
9. O. Meth-Cohn, B. Tarnowski, *Synthesis*, 1978, 56.
10. For examples, see: (a) O. Meth-Cohn, B. Tarnowski, *Adv. Heterocycl. Chem.*, 1980, **26**,115. (b) S. Kumar, B. K. Singh, N. Kalra, V. Kumar, A. Kumar, A. K. Prasad, H. G. Raj, V. S Parmar, B. Ghosh, *Bioorg. Medicinal. Chem*., 2005, **13**, 1605. (c) P. V. K. Reddy, P. N. Kumar, G. V. P. J. Chandramouli, *Heterocyclic Chem.*, 2005, **42**, 283. (d) A. Maresca, C. Temperini, L. Pochet, B. Masereel, A. Scozzafava, C. T. Supuran, *J. Med. Chem*., 2010, **53**, 335.
11. S. Y. Peng, L. Wang, H. B. Guo, S. F. Sun, J. Wang, *Org. Biomol. Chem*., 2012, **10**, 2537.