EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Metal-free synthesis of furocoumarins: A new approach via iodine-promoted one-pot cyclization between 4-hydroxycoumarins and acetophenones

Authors: Nam Thanh Son Phan, Phuc Pham, Que Nguyen, Nhu Tran, Vu Nguyen, Son Doan, Hiep Ha, and Thanh Truong

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800983

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800983

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201800983

WILEY-VCH

Metal-free synthesis of furocoumarins: A new approach via iodine-promoted one-pot cyclization between 4-hydroxycoumarins and acetophenones

Phuc H. Pham,[a] Que T. D. Nguyen,[a] Nhu K. Q. Tran, [a] Vu H. H. Nguyen,[a] Son. H. Doan,[a] Hiep Q. Ha,[a] Thanh Truong,[a] and Nam T. S. Phan*[a]

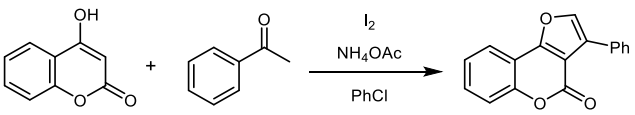
Dedication ((optional))

Abstract: A new transition metal-free approach was developed to achieve substituted furocoumarins via iodine-promoted one-pot cyclization between 4-hydroxycoumarins and acetophenones. High yields of furocoumarins were achieved in the presence of NH_4OAc as an additive, while neither acidic nor basic additives were effective. The reaction would proceed via *5-exo-tet* cyclization but not O-alkylation. The fact that commercially available starting materials could be used without the need of transition metal catalyst would be of significant advantages.

Coumarins have emerged as one of the most recognizable scaffolds, existing in many natural products and pharmaceuticals [1, 2]. Among numerous heterocyclic fused coumarins, furocoumarins have received significant attention owing to their essential medicinal values [3, 4]. Accordingly, a variety of protocols have been explored to synthesize these bicyclic scaffolds. Cheng et al. previously synthesized furocoumarins via a $Pd(OAc)_2$-catalyzed intramolecular cross dehydrogenative coupling transformation [5]. Bankar et al. Bankar et al. achieved furocoumarins by utilizing a cascade transacetalisation, Fries-type rearrangement followed by Michael addition and ring-opening aromatization [6]. Yang et al. demonstrated a useful one-pot protocol for the synthesis of furocoumarins via an acylation of phosphorus zwitterions and a successive intramolecular Wittig reaction [7]. Ghosh and Hajra obtained furocoumarins via a DABCO-promoted cyclization transformation of 4-hydroxycoumarins and nitrostyrenes [8]. Iodine has recently emerged as a promising alternative for many transition metals due to its ability to promote a variety of organic transformations [9-12]. In this communication, we would like to report a new iodine-promoted one-pot cyclization transformation between acetophenones and 4-hydroxycoumarins to achieve corresponding furocoumarins.

The reaction between 4-hydroxycoumarin and acetophenone was investigated (Scheme 1). It was noted that 3-phenyl-4H-furo[3,2-c]chromen-4-one was detected in the presence of I_2 and NH_4OAc. Initial studies focused on screening reaction conditions to improve the yield of the furocoumarin (Table 1). The reaction was conducted in chlorobenzene for 12 h, with 1 equivalent of acetophenone, in the presence of 2 equivalents of I_2 and 3 equivalents of NH_4OAc. The influence of temperature was explored (Entries 1-4, Table 1), and the result indicated the reaction should be performed at 120 °C with 56% yield being recorded (Entry 3, Table 1). The transformation was not favored by using excess amount of acetophenone, while the yield was significantly upgraded in the presence of excess 4-hydroxycoumarin (Entries 5-10, Table 1). With 3 equivalents of 4-hydroxycoumarin, 72% yield of 3-phenyl-4H-furo[3,2-c]chromen-4-one was achieved (Entry 10, Table 1). One crucial factor for the reaction between 4-hydroxycoumarin and acetophenone was the amount of I_2 (Entries 11-16, Table 1). Noted that no evidence of the desired product was detected in the absence of I_2, thus verifying the requirement of I_2 for this transformation (Entry 11, Table 1). Best yield was observed for the reaction utilizing 2 equivalents of I_2 (Entry 14, Table 1), and increasing the amount of I_2 did not result in higher yield.

The one-pot cyclization reaction between 4-hydroxycoumarin and acetophenone did not proceed in the absence of NH_4OAc as an additive. Therefore, several additives were tested for the formation of the furocoumarin, including basic, acidic, and neutral candidates (Entries 17-23). Indeed, neither acidic nor basic additives were appropriate for this reaction, generating the furocoumarin in very low yield. Among these additives, NH_4OAc and NH_4HCO_3 were effective for the one-pot cyclization, affording the expected product in 72% and 71% yields, respectively (Entries 21-22, Table 1). Additionally, the amount of NH_4OAc displayed a noticeable impact on the formation of 3-phenyl-4H-furo[3,2-c]chromen-4-one (Entries 24-28, Table 1). Noted that only 3% yield was detected in the absence of NH_4OAc (Entry 24, Table 1), while expanding the amount of NH_4OAc to 5 equivalents improved the yield to 80% (Entry 28, Table 1). One important factor to be considered for the one-pot cyclization reaction was the reaction



Scheme 1. Iodine-mediated one-pot synthesis of 3-phenyl-4H-furo[3,2-c]chromen-4-one.

Table 1. Screening of reaction conditions[a].

[a] Phuc H. Pham, Que T. D. Nguyen, Nhu K. Q. Tran, Vu H. H. Nguyen, Son. H. Doan, Hiep Q. Ha, Thanh Truong, Nam T. S. Phan
Faculty of Chemical Engineering
HCMC University of Technology, VNU-HCM
268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Viet Nam
E-mail: ptsnam@hcmut.edu.vn

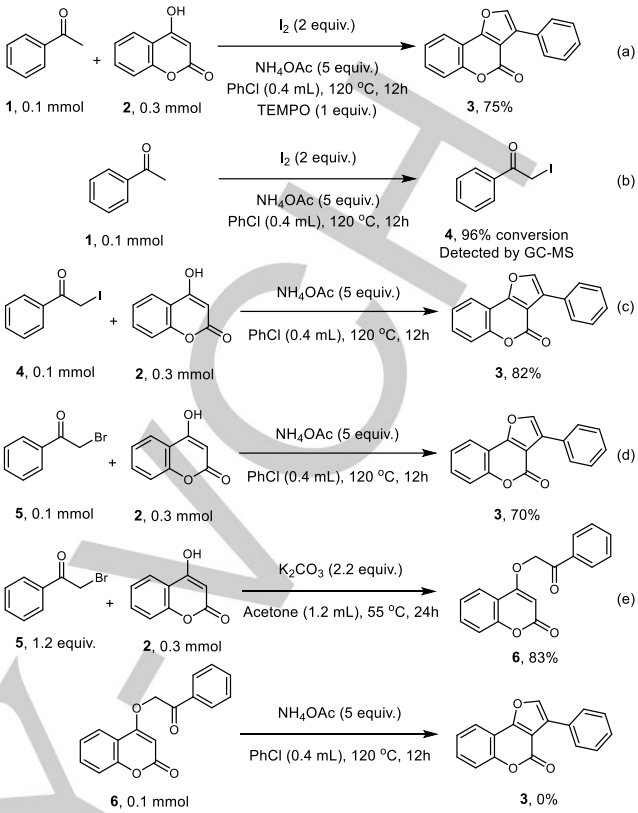
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Entry	Reactant ratio[b]	I_2 (equiv.)	Additive (equiv.)	Solvent	Yield[c]
1	1:1	2	NH_4OAc (3)	PhCl	8[d]
2	1:1	2	NH_4OAc (3)	PhCl	33[e]
3	1:1	2	NH_4OAc (3)	PhCl	54
4	1:1	2	NH_4OAc (3)	PhCl	56[f]
5	1:2	2	NH_4OAc (3)	PhCl	44
6	1:3	2	NH_4OAc (3)	PhCl	11
7	1:4	2	NH_4OAc (3)	PhCl	7
8	2:1	2	NH_4OAc (3)	PhCl	60
9	3:1	2	NH_4OAc (3)	PhCl	72
10	3:1	0	NH_4OAc (3)	PhCl	0
11	3:1	1	NH_4OAc (3)	PhCl	30
12	3:1	1.5	NH_4OAc (3)	PhCl	59
13	3:1	2	NH_4OAc (3)	PhCl	72
14	3:1	2.5	NH_4OAc (3)	PhCl	72
15	3:1	3	NH_4OAc (3)	PhCl	71
16	3:1	2	Et_3N (3)	PhCl	1
17	3:1	2	DMAP (3)	PhCl	8
18	3:1	2	K_2CO_3 (3)	PhCl	9
19	3:1	2	NaOAc (3)	PhCl	2
20	3:1	2	NH_4OAc (3)	PhCl	72
21	3:1	2	NH_4HCO_3 (3)	PhCl	71
22	3:1	2	HOAc (3)	PhCl	0
23	3:1	2	NH_4OAc (0)	PhCl	3
24	3:1	2	NH_4OAc (2)	PhCl	46
25	3:1	2	NH_4OAc (3)	PhCl	72
26	3:1	2	NH_4OAc (4)	PhCl	76
27	3:1	2	NH_4OAc (5)	PhCl	80
28	3:1	2	NH_4OAc (5)	n-BuOH	8
29	3:1	2	NH_4OAc (5)	DMF	3
30	3:1	2	NH_4OAc (5)	dioxane	26
31	3:1	2	NH_4OAc (5)	toluene	62
32	3:1	2	NH_4OAc (5)	xylene	73
33	3:1	2	NH_4OAc (5)	DCB	34
34	3:1	2	NH_4OAc (5)	PhCl	80
35	3:1	2	NH_4OAc (5)	PhCl	83[g]

[a] Reaction conditions: 4-hydroxycoumarin (0.3 mmol); solvent (0.5 mL); argon atmosphere; 120 °C; 12 h; Et_3N: triethylamine; DMAP: 4-dimethylaminopyridine; PhCl: chlorobenzene; DMF: N,N-dimethylformamide; DCB: 1,2-dichlorobenzene. [b] 4-hydroxycoumarin:acetophenone molar ratio. [c] GC yield. [d] 80 °C. [e] 100 °C. [f] 140 °C. [g] 0.4 mL PhCl.

solvent. A variety of solvents were tested for the transformation (Entries 29-35, Table 1), and chorobenzene emerged as the best solvent with 80% yield being noted (Entry 35, Table 1). Furthermore, changing the solvent amount from 0.5 mL to 0.4 mL also upgraded the yield of 3-phenyl-4H-furo[3,2-c]chromen-4-one to 83% (Entry 36, Table 1).

Following this protocol, several substituted furocoumarins were then synthesized (Table 2).). The reaction was conducted at 120 °C in chlorobenzene for 12 h, with 3 equivalents of 4-hydroxycoumarins, in the presence of 2 equivalents of I_2 and 5 equivalents of NH_4OAc. In the first series, the reaction between 4-hydroxycoumarin and several substituted acetophenones were explored (Entries 1-8, Table 2). The iodine-promoted one-pot cyclization between 4-hydroxycoumarin and acetophenone afforded 3-phenyl-4H-furo[3,2-c]chromen-4-one in 79% isolated yield (Entry 1). Moving to halo-substituted acetophenones, 3-(4-

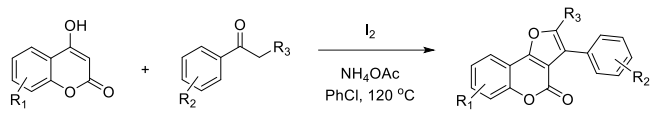


Scheme 2. Control experiments.

fluorophenyl)-4H-furo[3,2-c]chromen-4-one (Entry 2), 3-(4-chlorophenyl)-4H-furo[3,2-c]chromen-4-one (Entry 3), and 3-(4-bromophenyl)-4H-furo[3,2-c]chromen-4-one (Entry 4) were achieved in 90%, 88%, and 84% yields, respectively. Similarly, 3-(p-tolyl)-4H-furo[3,2-c]chromen-4-one was generated in 92% yield (Entry 5). However, methoxy-substituted acetophenones were noted to be less reactive towards the cyclization reaction (Entries 6-8). The transformation of 1-(thiophen-2-yl)ethan-1-one afforded the desired furocoumarin in 68% yield (Entry 9, Table 2). Propiophenone was also reactive towards the reaction, producing 2-methyl-3-phenyl-4H-furo[3,2-c]chromen-4-one in 84% yield (Entry 10, Table 2). Several substituted propiophenones and 4-hydroxycoumarins were utilized, and corresponding furocoumarins were obtained in high yields (Entries 11-17, Table 2). Propiophenone bearing strong electron-withdrawing group was also well tolerated, and 2-methyl-3-(3-nitrophenyl)-4H-furo[3,2-c]chromen-4-one was isolated in 87% yield (Entry 18, Table 2). This protocol was also effective for cyclohexanone, forming 7,8,9,10-tetrahydro-6H-benzofuro[3,2-c]chromen-6-one in 80% yield (Entry 19, Table 2). Interestingly, when α-tetralone was used as a sterically hindered substrate, subsequent aromatization occurred to give 6H-naphtho[1',2':4,5]furo[3,2-c]chromen-6-one in 26% yield (Entry 20, Table 2).

In order to achieve more information for the pathway of the one-pot cyclization reaction between acetophenone (**1**) and 4-hydroxycoumarin (**2**), necessary control experiments were then

Table 2. Iodine-promoted one-pot synthesis of substituted furocoumarins[a].



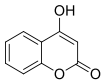
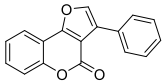
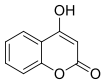
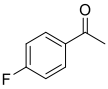
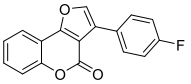
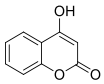
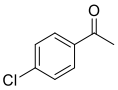
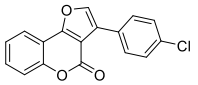
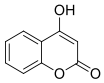
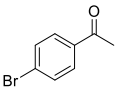
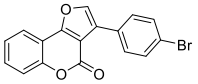
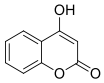
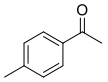
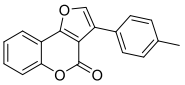
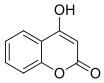
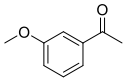
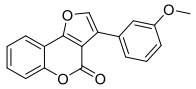
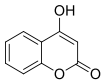
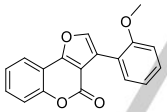
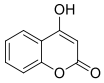
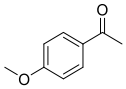
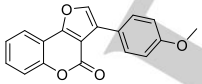
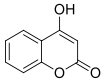
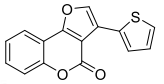
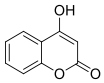
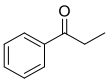
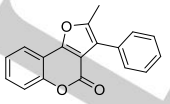
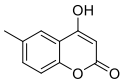
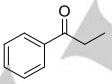
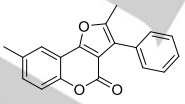
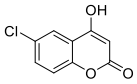
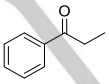
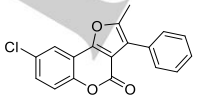
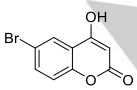
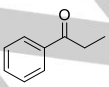
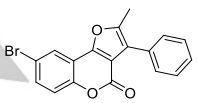
Entry	Reactant 1	Reactant 2	Product	Yield[b] (%)
1				79
2				90
3				88
4				84
5				92
6				53
7				28
8				54
9				68
10				84
11				85
12				84
13				81
14				75

Table 2 (continue)

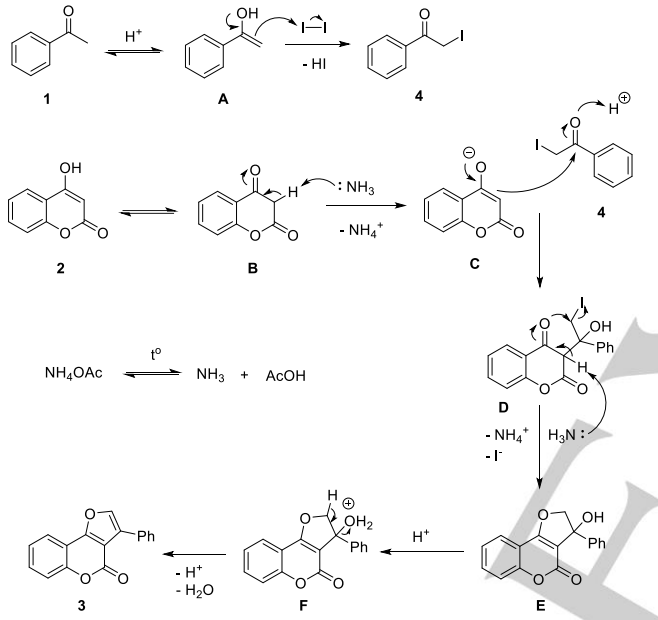
Entry	Reactant 1	Reactant 2	Product	Yield[b] (%)
15				76
16				78
17				72
18				87
19				80
20				26

[a)] Reaction conditions: 4-hydroxycoumarins (0.3 mmol); acetophenones (0.1 mmol); I_2 (0.2 mmol); NH_4OAc (0.5 mmol); chlorobenzene (0.4 mL); 120 °C; 12 h. [b)] Isolated yield.

performed (Scheme 2). (i) The reaction afforded 75% yield of 3-phenyl-4H-furo[3,2-c]chromen-4-one (**3**) in the presence of 1 equivalent of (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) as a radical scavenger, suggesting that the transformation did not follow a radical mechanism (Scheme 2 a). (ii) Heating (**1**) without (**2**) under the standard conditions led to the formation of 2-iodoacetophenone (**4**) with 96% conversion (Scheme 2 b). (iii) The reaction between (**2**) and (**4**) produced (**3**) in 82% yield in the presence of NH_4OAc under the standard conditions (Scheme 2 c). (iv) Utilizing similar conditions, the reaction between (**2**) and 2-bromoacetophenone (**5**) afforded 70% yield of (**3**) (Scheme 2 d). (v) 4-(2-Oxo-2-phenylethoxy)-2H-chromen-2-one (**6**) was prepared in 83% yield via the O-alkylation reaction between (**2**) and 2-bromoacetophenone (**5**) in the presence of K_2CO_3. However, upon heating (**6**) under the standard conditions, the desired furocoumarin (**3**) was not detected in the reaction mixture (Scheme 2 e), indicating that the one-pot cyclization reaction between (**1**) and (**2**) to produce (**3**) would not proceed via the formation of (**6**).

On the basis of above observations and the literature, a possible reaction pathway was suggested for the iodine-promoted one-pot cyclization between 4-hydroxycoumarin and acetophenone (Scheme 3). Initially, (**1**) was converted to (**4**) via its enol form (**A**) in the presence of an acid catalyst. Ammonia and acetic acid were produced upon heating the reaction mixture. Noted that neither acidic nor basic additives were appropriate, while NH_4OAc was effective due to the formation of

both acidic and basic species during the transformation. GC-MS analysis indicated the formation of (**4**) in the product mixture. Indeed, this transformation was previously demonstrated by Rao and Jadhav [13]. In the presence of NH_3 as a base, (**2**) was transformed to its enolate (**C**) via its active diketone form (**B**). Subsequently, nucleophilic addition of enolate (**C**) to (**4**) led to the formation of intermediate 3-(1-hydroxy-2-iodo-1-phenylethyl)chromane-2,4-dione (**D**). The base-promoted *5-exo-tet* cyclization consequently occurred to form intermediate 3-hydroxy-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**E**). Finally, the desired furocoumarin (**3**) was generated via an acid-catalyzed dehydration step. Indeed, Risitano et al. previously synthesized furocoumarins from 4-hydroxycoumarins and α-haloketones, and proposed that these tandem transformations would proceed



Scheme 3. Plausible reaction mechanism.

following two different pathways: (i) via O-alkylation, and (ii) via *5-exo-tet* cyclization [14]. Prakash et al. initially considered two plausible pathways for similar reactions, and finally suggested that the transformation did not proceed via O-alkylation step [15]. However, in this work, the iodine-promoted one-pot cyclization would not proceed via the O-alkylation (Scheme 2 e).

In conclusion, a new transition metal-free approach was developed to achieve substituted furocoumarins via iodine-promoted one-pot cyclization between 4-hydroxycoumarins and acetophenones. The transformation proceeded readily to produce furocoumarins in the presence of NH_4OAc as an additive, while neither acidic nor basic additives were effective. The solvent displayed a noticeable impact on the reaction, and chlorobenzene emerged as the best candidate. The reaction would proceed via *5-exo-tet* cyclization but not O-alkylation. The remarkable advantages of this protocol are: (i) no transitional metal is required; (ii) commercially available acetophenones and 4-hydroxycoumarins; (iii) high yields of furocoumarins; and (iv) broad substrate scope. This protocol would attract attention from the pharmaceutical and fine chemical industries.

Experimental Section

To a 8-mL screw-cap vial containing 0.4 mL chlorobenzene was added acetophenone (12.0 mg, 0.1 mmol), 4-hydroxycoumarin (48.6 mg, 0.3 mmol), NH_4OAc (38.5 mg, 0.5 mmol), molecular iodine (50.8 mg, 0.2 mmol) and diphenyl ether (17.0 mg, 0.1 mmol) as an internal standard. The reaction tube was then stirred at 120 °C for 12 h. After that, the mixture was slowly cooled to room temperature and washed with $Na_2S_2O_3$ solution (10% in water, 3×5 mL), the organic components was subsequently extracted into dichloromethane (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel with hexane/dichloromethane as eluent to give pure product. The product identity was further confirmed by GC-MS, ^1H NMR and ^{13}C NMR.

Acknowledgements ((optional))

Keywords: furocoumarins • 4-hydroxycoumarins • acetophenones • one-pot • tandem reaction

[1] Zhang, R.-R.; Liu, J.; Zhang, Y.; Hou, M.-Q.; Zhang, M.-Z.; Zhou, F.; Zhang, W.-H. *Eur. J. Med. Chem.* **2016,** *116*, 76.
[2] Kawaai, K.; Yamaguchi, T.; Yamaguchi, E.; Endo, S.; Tada, N.; Ikari, A.; Itoh, A. *J. Org. Chem.* **2018,** *83*, 1988.
[3] Medina, F. G.; Marrero, J. G.; Macías-Alonso, M.; González, M. C.; Córdova-Guerrero, I.; García, A. G. T.; Osegueda-Robles, S. *Nat. Prod. Rep.* **2015,** *32*, 1472.
[4] Melough, M. M.; Vance, T. M.; Lee, S. G.; Provatas, A. A.; Perkins, C.; Qureshi, A.; Cho, E.; Chun, O. K. *J. Agric. Food Chem.* **2017,** *65*, 3006.
[5] Cheng, C.; Chen, W.-W.; Xu, B.; Xu, M.-H. *Org. Chem. Front.* **2016,** *3*, 1111.
[6] Bankar, S. K.; Mathew, J.; Ramasastry, S. S. V. *Chem. Commun.* **2016,** *52*, 5569.
[7] Yang, S. M.; Wang, C. Y.; Lin, C. K.; Karanam, P.; Reddy, G. M.; Tsai, Y. L.; Lin, W. *Angew. Chem. Int. Ed.* **2018,** *57*, 1668.
[8] Ghosh, M.; Hajra, A. *Eur. J. Org. Chem.* **2015,** *35*, 7836.
[9] Donthiboina, K.; Namballa, H. K.; Shaik, S. P.; Nanubolu, J. B.; Shankaraiah, N.; Kamal, A. *Org. Biomol. Chem.* **2018,** *16*, 1720.
[10] Kour, D.; Gupta, A.; Kapoor, K. K.; Gupta, V. K.; Rajnikant; Singh, D.; Das, P. *Org. Biomol. Chem.* **2018,** *16*, 1330.
[11] Yang, J.; Xie, D.; Zhou, H.; Chen, S.; Huo, C.; Li, Z. *Org. Chem. Front.* **2018,** *5*, 1325.
[12] Xu, H.; Liu, H.-W.; Lin, H.-S.; Wang, G.-W. *Chem. Commun.* **2017,** *53*, 12477.
[13] Rao, M. L. N.; Jadhav, D. N. *Tetrahedron Lett.* **2006,** *47*, 6883.
[14] Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Tetrahedron Lett.* **2001,** *42*, 3503.
[15] Prakash, O.; Wadhwa, D.; Hussain, K.; Kumar, R. *Synth. Commun.* **2012,** *42*, 2947.

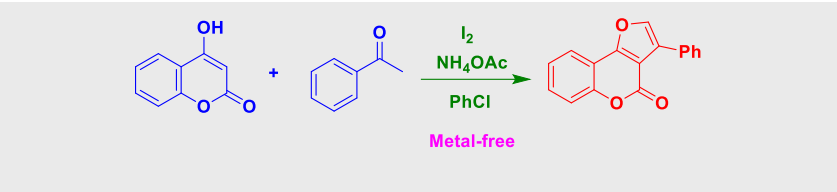
10.1002/ejoc.201800983

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



*Phuc H. Pham, Que T. D. Nguyen, Nhu K. Q. Tran, Vu H. H. Nguyen, Son. H. Doan, Hiep Q. Ha, Thanh Truong, and Nam T. S. Phan**

Page No. – Page No.

Metal-free synthesis of furocoumarins: A new approach via iodine-promoted one-pot cyclization between 4-hydroxycoumarins and acetophenones

Iodine-mediated one-pot synthesis of furocoumarins