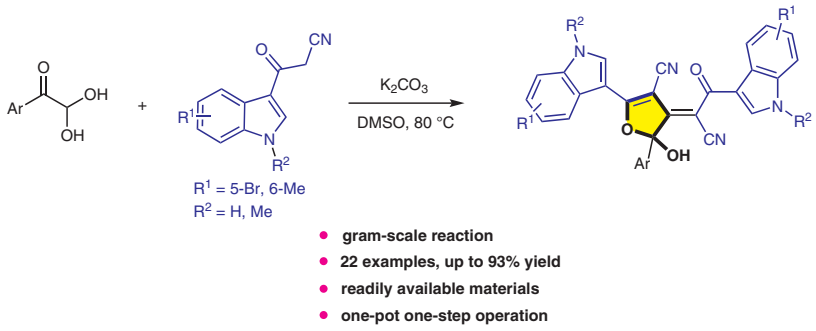
Synlett Q. Cai et al. Letter

Base-Promoted Tandem Cyclization for the Synthesis of Polyfunctional 2-Hydroxy-2,3-dihydrofurans from Arylglyoxal Monohydrates and 3-(1*H*-Indol-3-yl)-3-oxopropanenitrile

Qun Cai[a]
Hui-Yang Sheng[a]
Deng-Kui Li[b]
Yi Liu[*a]
An-Xin Wu[*b]

[a] Coal Conversion and New Carbon Materials Key Laboratory of Hubei Province, School of Chemistry and Chemical Engineering, Wuhan University of Science and Technology, Wuhan 430081, P. R. of China
yiliuchem@whu.edu.cn
[b] Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. of China
chwuax@mail.ccnu.edu.cn



Received: 01.05.2018
Accepted after revision: 12.06.2018
Published online: 09.08.2018
DOI: 10.1055/s-0037-1609555; Art ID: st-2018-w0281-l

Abstract An efficient base-promoted tandem cyclization for the synthesis of polyfunctional 2-hydroxy-2,3-dihydrofurans from arylglyoxal monohydrates and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile has been established. The investigation of the mechanism suggested that this reaction proceeds through a Knoevenagel condensation–Michael addition–oxidation–cyclization sequence. This method demonstrates the compatibility with a wide range of functional groups to produce the 2-hydroxy-2,3-dihydrofuran scaffolds in good to excellent yields in one pot.

Key words 2-hydroxy-2,3-dihydrofurans, tandem cyclization, arylglyoxal monohydrates, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile, one pot

The synthesis of *O*-heterocyclic compounds is a long-standing and continuing research topic due to their physicochemical and pharmacological properties with potential applications in the field of medicinal chemistry.[1] Among them, 2-hydroxy-2,3-dihydrofuran derivatives, serving as an important class of *O*-heterocyclic scaffolds, can be found in numerous natural products such as auranfuron A, auranfuron B, siphonarienfuranone, drimanes, alphitonin, and marsupsin (Figure 1).[2] Thus they have been reported to possess a wide spectrum of biological activities like antifungal, antitumor, antibiotic, bacteriostatic, and cytotoxic properties.[3–7] Besides, 2-hydroxy-2,3-dihydrofurans have also been used as unique synthetic intermediates for the preparation of more complex functional material molecules.[8]

Due to their great value, various approaches for 2-hydroxy-2,3-dihydrofuran derivatives have been developed. The main and classical synthetic methods focused on the reaction of aldehydes and/or ketones. For example, Kalesse and co-workers reported a three-step procedure to synthesize 2-hydroxy-2,3-dihydrofurans from aldehyde and diethyl ketone through intramolecular cyclization and meth-

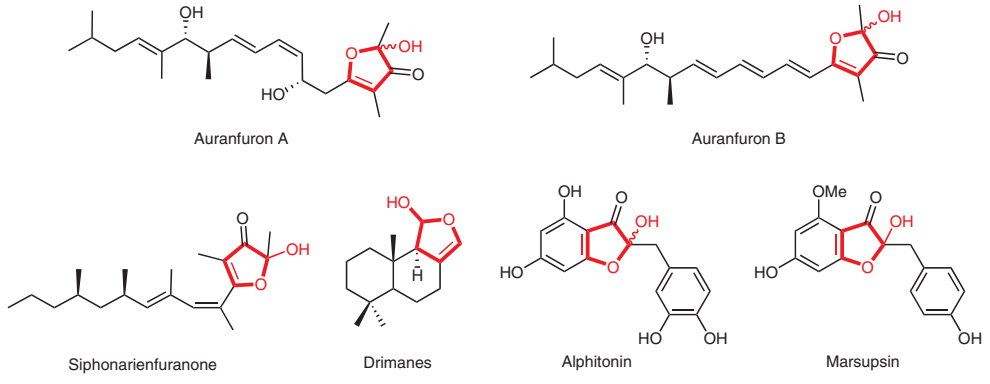
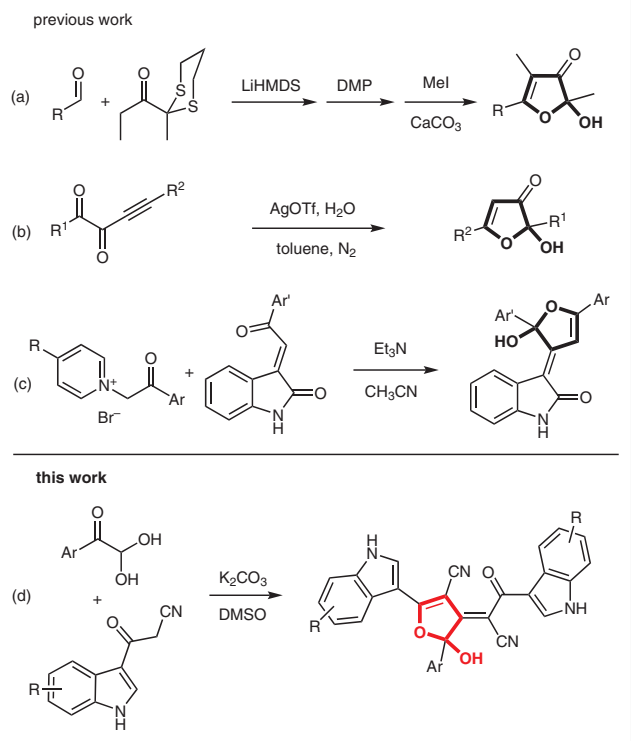


Figure 1 Selected natural products and pharmaceutical compounds containing a 2-hydroxy-2,3-dihydrofuran skeleton

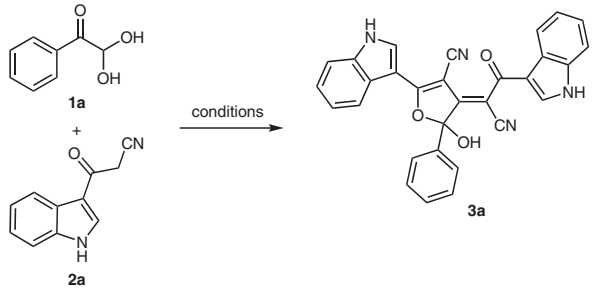
ylation (Scheme 1, a).[9] The Jiang group developed an AgOTf-catalyzed intramolecular ring closing of ynedione to furnish 2-hydroxy-2,3-dihydrofuran derivatives under nitrogen conditions (Scheme 1, b).[10] In addition, the Yan group reported a Michael addition and cyclization to achieve 2-hydroxy-2,3-dihydrofuran derivatives from pre-prepared pyridinium salts and 3-phenacylideneoxindoles (Scheme 1, c).[11] Despite these significant advances made to date,[12] the development of simple and practical synthetic strategies to access polyfunctional 2-hydroxy-2,3-dihydrofurans is still highly desirable. We herein report a base-promoted tandem cyclization to construct diversely substituted 2-hydroxy-2,3-dihydrofurans from arylglyoxal monohydrates and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile in one pot (Scheme 1, d). The advantages of this method include the use of readily available starting materials, metal-free catalysts, mild reaction conditions, one-step operation, and easy workup.



Scheme 1 Protocols for the synthesis of 2-hydroxy-2,3-dihydrofurans

Our study commenced with the tandem cyclization reaction of phenylglyoxal monohydrate (**1a**) and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**2a**) in the presence of different bases and solvents to optimize the reaction conditions (Table 1). Initially, we treated the substrate **1a** (0.5 mmol) and **2a** (1.0 mmol) with K_2CO_3(1.0 mmol) in EtOH at 80 °C (Table 1, entry 1), the desired product **3a** was obtained in 30% yield. A range of different solvent (*i*-PrOH, *t*-BuOH, CH_3CN, DMSO, DMF, DCE, THF) were screened, and DMSO was shown to be the most effective in this reaction (Table 1, entries 2–8). Then, several bases were screened for this domino reaction, such as Cs_2CO_3, $NaHCO_3$, NaOH, K_3PO_4, TEA, piperidine, and K_2CO_3. Still, K_2CO_3 showed the highest activity for this reaction (Table 1, entries 9–15). Improving or decreasing the reaction temperature would not increase the yield of target product (Table 1, entries 16–18), as well as the equivalent of K_2CO_3(Table 1, entries 19 and 20). Based on the experiments described above, the optimal reaction conditions were determined as follows: **1a** (0.5 mmol), **2a** (1.0 mmol), and K_2CO_3(1.0 mmol) in 3 mL of DMSO at 80 °C in a sealed vessel for 2 hours.

Table 1 Optimization of the Reaction Conditions for the Synthesis of **3a**[a]

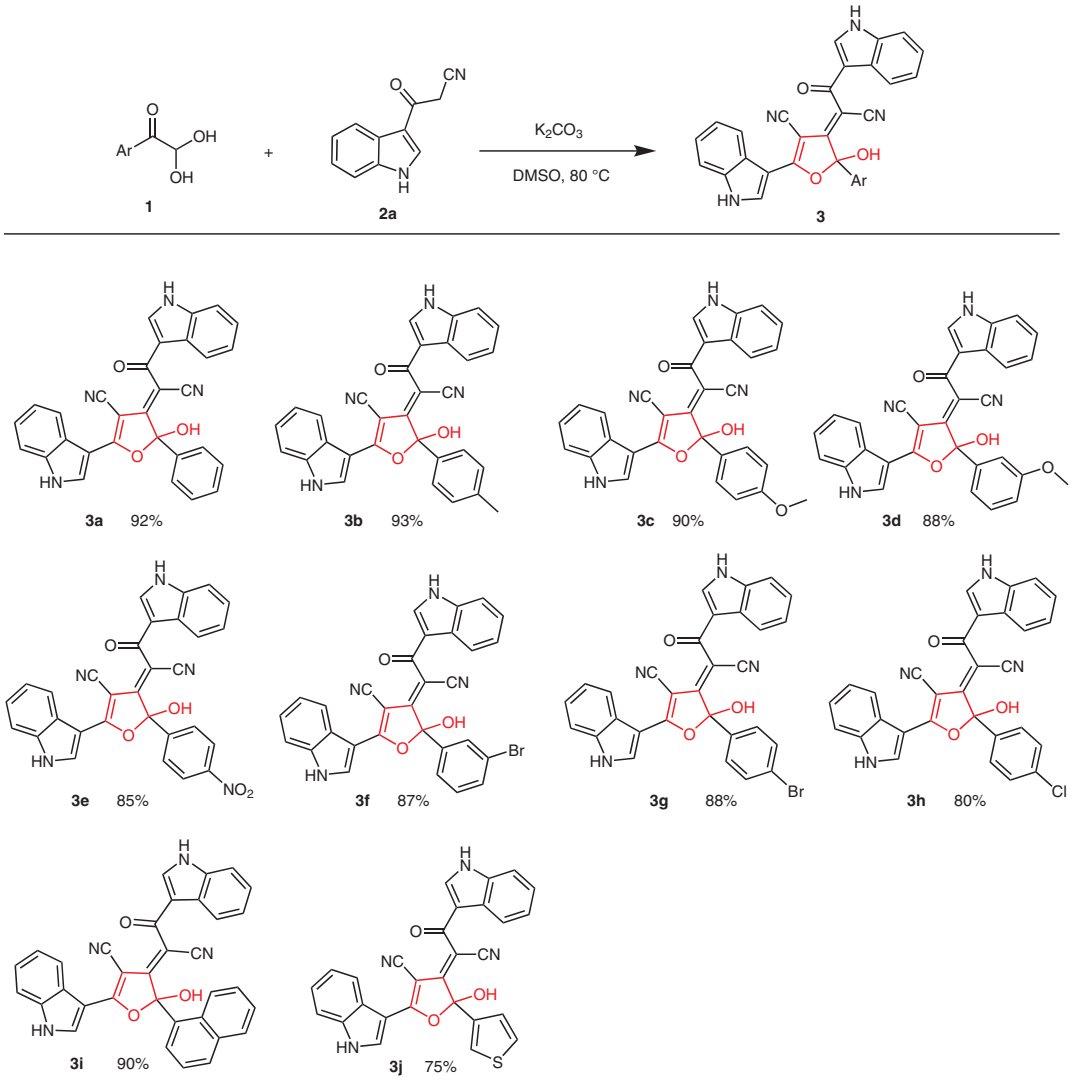


Entry	Solvent	Base	Amount of base (equiv)	Temp (°C)	Yield (%)[b]
1	EtOH	K_2CO_3	2	80	30
2	*i*-PrOH	K_2CO_3	2	80	22
3	*t*-BuOH	K_2CO_3	2	80	<10
4	CH_3CN	K_2CO_3	2	80	11
5	DMSO	K_2CO_3	2	80	92
6	DMF	K_2CO_3	2	80	<10
7	DCE	K_2CO_3	2	80	0
8	THF	K_2CO_3	2	80	0
9	DMSO	–	–	80	0
10	DMSO	Cs_2CO_3	2	80	22
11	DMSO	$NaHCO_3$	2	80	33
12	DMSO	NaOH	2	80	45
13	DMSO	K_3PO_4	2	80	47
14	DMSO	TEA	2	80	16
15	DMSO	piperidine	2	80	0
16	DMSO	K_2CO_3	2	rt	21
17	DMSO	K_2CO_3	2	60	80
18	DMSO	K_2CO_3	2	100	70
19	DMSO	K_2CO_3	1.5	80	82
20	DMSO	K_2CO_3	2.5	80	90

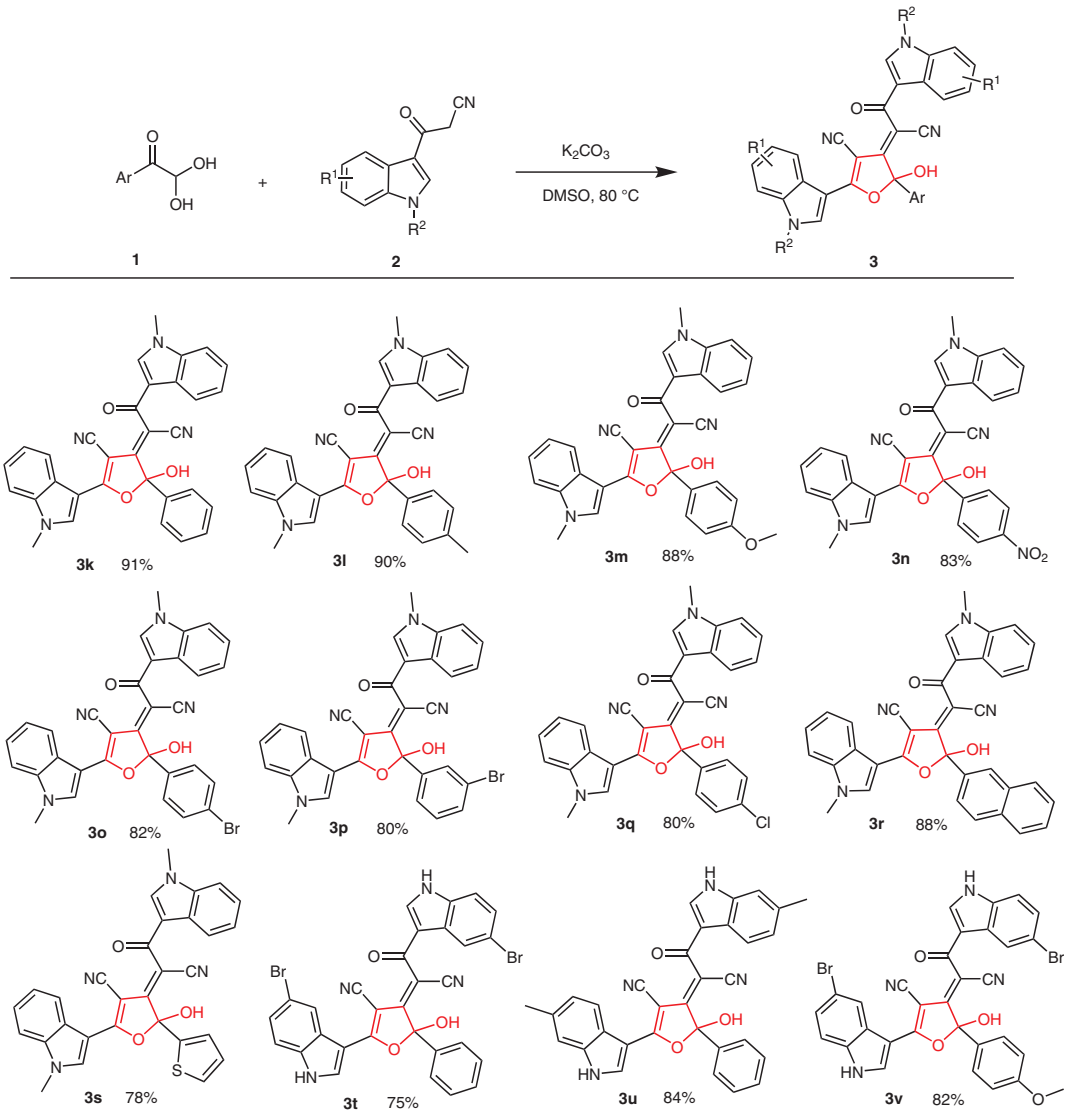
[a]Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.0 mmol, 2 equiv), and base (x equiv) were heated in 3 mL of solvent in a sealed vessel for 2 hours.
[b]Isolated yields.

With the optimized conditions in hand, we then extended the scope of this reaction, and the results are illustrated in Scheme 2. It is worth mentioning that the reaction demonstrated wide tolerance for diverse substituents of arylglyoxals. Arylglyoxals bearing electron-neutral (e.g., 4-H, 4-Me) and electron-rich (e.g., 3-OMe, 4-OMe) groups proceeded smoothly to give the corresponding products in excellent yields (88–93%, **3a–d**). Electron-deficient (e.g., 4-NO_2) and halogenated (e.g., 3-Br, 4-Br, 4-Cl) substituents were converted into the corresponding products in good yields (80–88%; **3e–h**). In addition, 2-naphthyl and heteroaryl (e.g., 3-thienyl) substituents could afford the products **3i** and **3j** in 90% and 75% yields, respectively.

Notably, 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (**2b**) could also be successfully applied in the convenient synthesis of the polyfunctional 2-hydroxy-2,3-dihydrofuran (Scheme 3). For example, **2b** could react smoothly with arylglyoxals containing electron-neutral (4-H, 4-Me) and electron-donating (4-OMe) groups to furnish the target products (88–91%; **3k–m**). Much to our satisfaction, electron-deficient (e.g., 4-NO_2) and halo-substituted (e.g., 4-Br, 3-Br, 4-Cl) arylglyoxals could also afford the desired products in excellent yields (80–83%, **3n–q**), which provided the possibility for further functionalization. Meanwhile, the optimized conditions could be applied to 2-naphthyl and 2-thienyl arylglyoxals to offer the corresponding products (**3r**,**s**, 78–88%). Furthermore, a variety of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with different substituents, such as 6-methyl and 5-bromo groups, were also explored. Gratifyingly, all proved to be compatible under



Scheme 2 Scope of arylglyoxals. *Reagents and conditions*: **1** (0.5 mmol), **2a** (1.0 mmol), K_2CO_3 (1.0 mmol) in DMSO (3 mL) at 80 °C for 2 hours.



Scheme 3 Scope of arylglyoxals and 3-(1*H*-indol-3-yl)-3-oxopropanenitriles. *Reagents and conditions*: **1** (0.5 mmol), **2** (1.0 mmol), K_2CO_3 (1.0 mmol) in DMSO (3 mL) at 80 °C for 2 hours.

the optimal conditions (75–84%; **3t–v**). The structure of **3q** was unambiguously confirmed by X-ray diffraction analysis (see Supplementary Information).

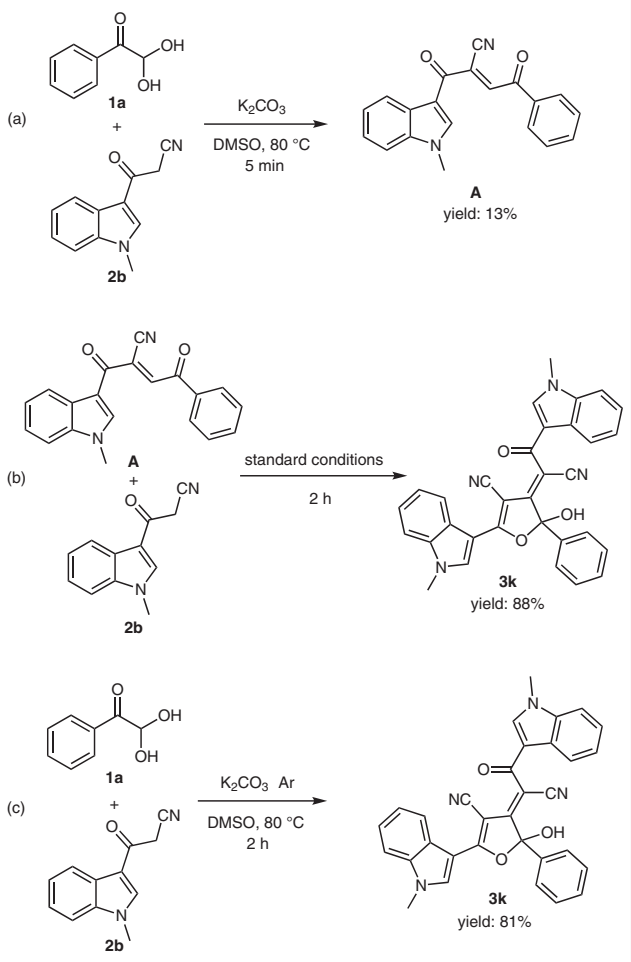
To gain some insight into the mechanism of this reaction, a series of control experiments were performed as shown in Scheme 4. Initially, the reaction of phenylglyoxal monohydrate **1a** and 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (**2b**) in 1:1 ratio was performed under the standard conditions. When the reaction stopped at 5 minutes, compound **A** was obtained in 13% yield (Scheme 4, a). Moreover, treatment of **A** with **2b** in 1:1 ratio under the standard conditions directly generated the target product **3k** in good yield (Scheme 4, b). These results clearly confirmed that **A** was the key intermediate in this transformation. Furthermore, when this reaction was conducted under an argon condition, the desired product **3k** was still isolated in 81% yield (Scheme 4, c), which indicated that DMSO might serve as double rules of solvent and oxidant for the synthesis of 2-hydroxy-2,3-dihydrofurans.

On the basis of experimental results above and the precedent literature,[13] a tandem process was proposed for the formation of 2-hydroxy-2,3-dihydrofuran **3** (**3a** as an example) in Scheme 5. Initially, intermediate **A′** was formed by means of a Knoevenagel condensation between phenylglyoxal monohydrate (**1a**) and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**2a**). Subsequently, another amount of **2a** reacted with **A′** to form intermediate **B** via a Michael addition.

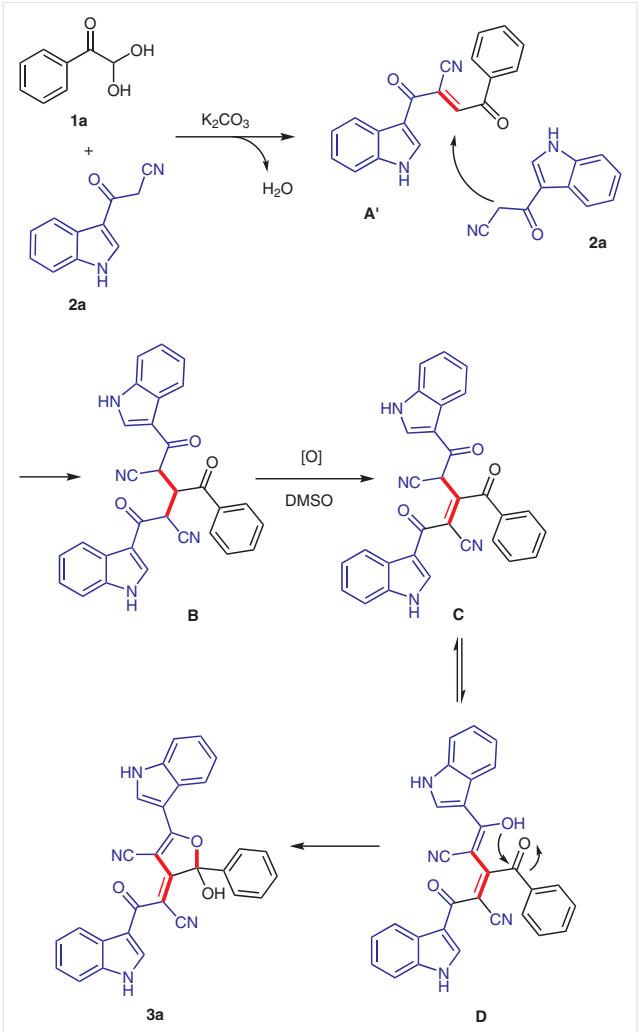
Finally, the intermediate **B** underwent oxidation, tautomerization, and intramolecular cyclization to form the final product **3a**.

To further make this reaction more attractive in terms of synthetic practicality, a gram-scale synthesis of 2-hydroxy-2,3-dihydrofuran (**3a**) was carried out. To our great pleasure, the reaction proceeded well and the desired product **3a** was isolated in 80% yield after 4 hours in DMSO at 80 °C (Scheme 6).

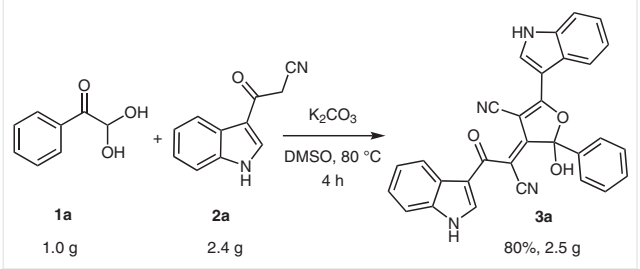
In conclusion, a convenient and efficient tandem-cyclization reaction has been established for the synthesis of 2-hydroxy-2, 3-dihydrofuran derivatives under mild conditions.[14] Initial studies of the mechanism suggest that this reaction occurred via a Knoevenagel condensation–Michael addition–oxidation–cyclization protocol. Moreover, the reaction is compatible with a variety of functionalities and is amenable to be scaled up to a gram scale. This practical synthetic strategy also demonstrates potential for the construction of complex heterocyclic compounds.



Scheme 4 Control experiments to prove the mechanism



Scheme 5 Possible mechanism



Scheme 6 Gram-scale experiment of product **3a**

Funding Information

21673166We would like to thank the National Natural Science Foundation of China (Grant 21272085, 21673166) for their generous financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609555.

References and Notes

(1) (a) Santos, E. A.; Quintela, A. L.; Ferreira, E. G.; Sousa, T. S.; Pinto, F.; Hajdu, E.; Carvalho, M. S.; Salani, S.; Rocha, D. D.; Wilke, D. V.; Torres Mda, C.; Jimenez, P. C.; Silveira, E. R.; La Clair, J. J.; Pessoa, O. D.; Costa-Lotufo, L. V. *J. Nat. Prod.* **2015**, *78*, 996. (b) Li, H.; Zhao, M.; Su, G.; Lin, L.; Wang, Y. *J. Agric. Food Chem.* **2016**, *64*, 4725. (c) Wegener, S.; Bornik, M. A.; Kroh, L. W. *J. Agric. Food Chem.* **2015**, *63*, 6457. (d) Mahidol, C.; Prawat, H.; Sangpetsiripan, S.; Ruchirawat, S. *J. Nat. Prod.* **2009**, *72*, 1870. (e) Tsukamoto, S.; Miura, S.; van Soest, R. W. M.; Ohta, T. *J. Nat. Prod.* **2003**, *66*, 438. (f) Ueda, A.; Yamamoto, A.; Kato, D.; Kishi, Y. *J. Am. Chem. Soc.* **2014**, *136*, 5171. (g) Oblak, E. Z.; VanHeyst, M. D.; Li, J.; Wiemer, A. J.; Wright, D. L. *J. Am. Chem. Soc.* **2014**, *136*, 4309. (h) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O.; Ianaro, A. *Tetrahedron* **1999**, *55*, 7045.

(2) For representative references, see: (a) Cho, J. Y.; Kwon, H. C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2006**, *69*, 425. (b) Bromley, C. L.; Popplewell, W. L.; Pinchuck, S. C.; Hodgson, A. N.; Davies-Coleman, M. T. *J. Nat. Prod.* **2012**, *75*, 497. (c) Montagnac, A.; Martin, M. T.; Debitus, C.; Païs, M. *J. Nat. Prod.* **1996**, *59*, 866. (d) Barrero, A. F.; Cortés, M.; Manzaneda, E. A.; Cabrera, E.; Chahboun, R.; Lara, M.; Rivas, A. R. *J. Nat. Prod.* **1999**, *62*, 1488. (e) Elsinghorst, P. W.; Cavlar, T.; Müller, A.; Braune, A.; Blaut, M.; Gütschow, M. *J. Nat. Prod.* **2011**, *74*, 2243. (f) Jahromi, M. A. F.; Ray, A. B.; Chansouria, J. P. N. *J. Nat. Prod.* **1993**, *56*, 989. (g) Manickam, M.; Ramanathan, M.; Farboodniay Jahromi, M. A.; Chansouria, J. P. N.; Ray, A. B. *J. Nat. Prod.* **1997**, *60*, 609. (h) Krenn, L.; Presser, A.; Pradhan, R.; Bahr, B.; Paper, D. H.; Mayer, K. K.; Kopp, B. *J. Nat. Prod.* **2003**, *66*, 1107.

(3) Schreiber, S. L.; Kelly, S. E.; Porco, J. A. Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210.

(4) Capon, R. J.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 2506.

(5) Okanya, P. W.; Mohr, K. I.; Gerth, K.; Kessler, W.; Jansen, R.; Stadler, M.; Müller, R. *J. Nat. Prod.* **2014**, *77*, 1420.

(6) Das, S.; Koley, P.; Pramanik, A. *Tetrahedron Lett.* **2011**, *52*, 3243.

(7) Bergeron, R. I.; Cavanaugh, P. F. Jr.; Kline, S. J.; Hughes, R. G. Jr.; Elliott, G. T.; Porter, C. W. *Biochem. Biophys. Res. Commun.* **1984**, *121*, 848.

(8) (a) Barjau, J.; Schnakenburg, G.; Waldvogel, S. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 1415. (b) Mukaiyama, T.; Ishikawa, H.; Koshino, H.; Hayashi, Y. *Chem. Eur. J.* **2013**, *19*, 17789. (c) Tyurin, R. V.; Kosygina, O. V.; Mezheritskii, V. V. *Russ. J. Org. Chem.* **2009**, *45*, 848. (d) Debnath, K.; Pathak, S.; Pramanik, A. *Tetrahedron Lett.* **2014**, *55*, 1743. (e) Hirose, S.; Tomatsu, K.; Yanase, E. *Tetrahedron Lett.* **2013**, *54*, 7040. (f) Suzuki, M.; Imai, K.; Wakabayashi, H.; Arita, A.; Johmoto, K.; Uekusa, H.; Kobayashi, K. *Tetrahedron* **2011**, *67*, 5500.

(9) Hartmann, O.; Kalesse, M. *Org. Lett.* **2012**, *14*, 3064.

(10) Zhang, Z. G.; Dai, Z. H.; Jiang, X. F. *Asian J. Org. Chem.* **2016**, *5*, 52.

(11) Fu, Q.; Yan, C.-G. *Tetrahedron* **2013**, *69*, 5841.

(12) (a) Smith, L. I.; Holum, J. R. *J. Am. Chem. Soc.* **1956**, *78*, 3417. (b) Hwu, J. R.; Sambaiah, T.; Chakraborty, S. K. *Tetrahedron Lett.* **2003**, *44*, 3167. (c) Peter, M.; Gleiter, R.; Rominger, F.; Oeser, T. *Eur. J. Org. Chem.* **2004**, 3212. (d) Jensen, K. L.; Franke, P. T.; Nielsen, L. T.; Daasbjerg, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 129. (e) Gao, Q. H.; Wu, X.; Liu, S.; Wu, A. X. *Org. Lett.* **2014**, *16*, 1732. (f) Uchida, R.; Lee, D.; Suwa, I.; Ohtawa, M.; Watanabe, N.; Demachi, A.; Ohte, S.; Katagiri, T.; Nagamitsu, T.; Tomoda, H. *Org. Lett.* **2017**, *19*, 5980.

(13) (a) Mase, N.; Horibe, T. *Org. Lett.* **2013**, *15*, 1854. (b) Su, C.; Chen, Z.-C.; Zhen, Q.-G. *Synthesis* **2003**, 555. (c) Ogiwara, Y.; Takahashi, K.; Kitazawa, T.; Sakai, N. *J. Org. Chem.* **2015**, *80*, 3101. (d) Yadav, J. S.; Reddy, B. S. S.; Basak, A. K.; Visali, B.; Narsaiah, A. V.; Nagaiah, K. *Eur. J. Org. Chem.* **2004**, 546.

(14) **Typical Procedure for the Synthesis of 3a**

A mixture of phenylglyoxal monohydrate (**1a**, 0.5 mmol), 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**2a**, 1.0 mmol), and K_2CO_3 (1.0 mmol) in DMSO (3 mL) was stirred at 80 °C for 2 h till almost completed conversion of the substrates by TLC analysis, then 30% NaCl solution (50 mL) was added to the mixture, which was then extracted with EtOAc three times (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **3a** (221.7 mg, 92%) as a yellow solid.

(*E*)-4-[2-(1*H*-Indol-3-yl)-2-oxoethylidene]-5-hydroxy-2-(1*H*-indol-3-yl)-5-phenyl-4,5-dihydrofuran-3-carbonitrile (3a)

Yield 92%, 221.7 mg; yellow solid; mp 255.5–257.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.75 (s, 1 H), 12.21 (s, 1 H), 9.65 (s, 1 H), 8.68 (s, 1 H), 8.22 (s, 1 H), 8.14 (d, *J* = 7.8 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.72–7.64 (m, 2 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.54–7.44 (m, 3 H), 7.33–7.23 (m, 4 H).^{13}C NMR (100 MHz, DMSO-d_6): δ = 180.1, 173.8, 159.6, 137.0, 136.7, 136.1, 136.0, 135.2, 129.6, 128.3, 125.6, 125.0, 124.7, 123.9, 123.3, 123.0, 122.2, 121.3, 121.2, 116.8, 115.7, 114.5, 113.2, 113.0, 112.4, 103.4, 96.6, 79.4. IR (KBr): 3424, 3265, 2208, 1610, 1523, 1483, 1430, 1307, 1235, 745 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{19}N_4O_3$: 483.1452; found: 483.1449.

(*E*)-4-[2-(1*H*-Indol-3-yl)-2-oxoethylidene]-5-hydroxy-2-(1*H*-indol-3-yl)-5-(4-nitrophenyl)-4,5-dihydrofuran-3-carbonitrile (3e)

Yield 85%, 224.0 mg; yellow solid; mp 249.3–250.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.84 (s, 1 H), 12.25 (s, 1 H), 10.07 (s, 1 H), 8.74 (s, 1 H), 8.44–8.34 (m, 2 H), 8.26 (s, 1 H), 8.20–8.13 (m, 1 H), 8.03–7.93 (m, 2 H), 7.86 (d, *J* = 6.0 Hz, 1 H), 7.68–7.61 (m, 1 H), 7.58–7.53 (m, 1 H), 7.35–7.22 (m, 4 H).^{13}C NMR (150 MHz, DMSO-d_6): δ = 180.1, 174.1, 159.1, 148.4, 143.4, 137.0, 136.3, 135.8, 127.6, 125.3, 124.8, 124.3, 123.9, 123.6, 123.4, 122.5, 122.3, 121.5, 121.4, 116.9, 115.8, 114.4, 113.5, 112.6, 111.7, 103.5, 96.9, 79.8. IR (KBr): 3387, 3256, 2205, 1607, 1563, 1525, 1427, 1348, 1304, 1235, 1206, 1143, 979, 744 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{18}N_5O_5$: 528.1302; found: 528.1296.

(*E*)-4-[2-(1*H*-Indol-3-yl)-2-oxoethylidene]-5-(4-chlorophenyl)-5-hydroxy-2-(1*H*-indol-3-yl)-4,5-dihydrofuran-3-carbonitrile (3h)

Yield 80%, 206.4 mg; yellow solid; mp 245.0–246.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.77 (s, 1 H), 12.20 (s, 1 H), 9.78 (s, 1 H), 8.68 (s, 1 H), 8.21 (s, 1 H), 8.14 (d, *J* = 5.4 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.67 (d, *J* = 7.2 Hz, 2 H), 7.63–7.49 (m, 4 H), 7.34–7.22 (m, 4 H).^{13}C NMR (150 MHz, DMSO-d_6): δ = 180.4, 174.2, 159.6, 136.4, 136.2, 135.6, 134.7, 128.7, 128.0, 125.4, 124.9, 124.3, 123.6, 123.3, 122.5, 121.5, 117.0, 115.9, 114.6, 113.5, 113.3, 112.6, 103.6, 96.8, 79.7, 56.2. IR (KBr): 3427, 2208, 1610, 1570, 1525, 1486, 1427, 1308, 1235, 1140, 745 cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{30}H_{17}ClN_4NaO_3$: 539.0881; found: 539.0885.

(*E*)-4-[2-(1*H*-Indol-3-yl)-2-oxoethylidene]-5-hydroxy-2-(1*H*-indol-3-yl)-5-(thiophen-3-yl)-4,5-dihydrofuran-3-carbonitrile (3j)

Yield 75%, 183.0 mg; yellow solid; mp 267.9–269.3 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.77 (s, 1 H), 12.26 (s, 1 H), 9.63 (s, 1 H), 8.73 (s, 1 H), 8.31 (s, 1 H), 8.25–8.18 (m, 1 H), 7.97 (d, *J* = 6.0 Hz, 1 H), 7.90 (s, 1 H), 7.67–7.61 (m, 2 H), 7.58 (d, *J* = 5.4 Hz, 1 H), 7.34–7.26 (m, 5 H).^{13}C NMR (150 MHz, DMSO-d_6): δ = 180.6, 173.8, 159.4, 138.8, 137.1, 136.4, 135.5, 135.4, 127.5, 125.8, 125.5, 125.0, 124.2, 123.6, 123.3, 122.6, 121.5, 117.1, 116.1, 116.0, 114.8, 113.5, 112.6, 111.7, 103.8, 96.8, 79.3. IR (KBr): 3260, 2204, 1613, 1568, 1509, 1481, 1434, 1304, 1237, 1207, 1146, 1023, 742 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{18}N_4O_3S$: 489.1016; found: 489.1015.

(*E*)-5-Hydroxy-2-(1-methyl-1*H*-indol-3-yl)-4-[2-(1-methyl-1*H*-indol-3-yl)-2-oxoethylidene]-5-phenyl-4,5-dihydrofuran-3-carbonitrile (3k)

Yield 91%, 232.1 mg; yellow solid; mp 244.1–245.2 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.65 (s, 1 H), 8.67 (s, 1 H), 8.20 (s, 1 H), 8.15 (d, *J* = 5.4 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.75–7.63 (m, 3 H), 7.60 (d, *J* = 7.2 Hz, 1 H), 7.55–7.46 (m, 3 H), 7.39–7.33 (m, 2 H), 7.32–7.27 (m, 2 H), 3.98 (s, 3 H), 3.91 (s, 3 H).^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.9, 173.6, 160.2, 139.0, 138.3, 137.6, 137.2, 137.0, 129.8, 128.5, 125.8, 125.7, 125.3, 124.2, 123.6, 123.5, 122.7, 121.6, 116.9, 114.7, 114.4, 113.1, 111.9, 111.0, 102.5, 96.5, 79.6, 34.1, 33.6. IR (KBr): 3437, 3226, 2189, 1580, 1535, 1471, 1365, 1244, 746 cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{32}H_{22}N_4NaO_3$: 533.1584; found: 533.1576.

(*E*)-5-(3-Bromophenyl)-5-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-4-[2-(1-methyl-1*H*-indol-3-yl)-2-oxoethylidene]-4,5-dihydrofuran-3-carbonitrile (3p)

Yield 80%, 235.6 mg; yellow solid; mp 235.4–237.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.85 (s, 1 H), 8.68 (s, 1 H), 8.19 (s, 1 H), 8.15 (d, *J* = 6.6 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.72 (d, *J* = 5.4 Hz, 1 H), 7.69 (d, *J* = 6.6 Hz, 1 H), 7.62–7.57 (m, 2 H), 7.50–7.45 (m, 1 H), 7.43–7.24 (m, 5 H), 3.99 (s, 3 H), 3.91 (s, 3 H).^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.7, 173.6, 159.8, 139.5, 139.1, 138.6, 138.5, 137.6, 137.5, 137.1, 132.9, 131.0, 128.7, 125.7, 125.2, 125.0, 124.3, 123.7, 123.6,122.6, 121.6, 116.9, 114.7, 114.3, 111.9, 111.1, 102.5, 96.5, 79.8, 34.2, 33.6. IR (KBr): 3443, 2197, 1522, 1462, 1363, 1321, 1226, 1087, 748 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{32}H_{22}BrN_4O_3$: 589.0870; found: 589.0877.

(*E*)-5-Hydroxy-2-(1-methyl-1*H*-indol-3-yl)-4-[2-(1-methyl-1*H*-indol-3-yl)-2-oxoethylidene]-5-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (3r)

Yield 88%, 246.4 mg; yellow solid; mp 228.8–230.0 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.84 (s, 1 H), 8.68 (s, 1 H), 8.18 (s, 1 H), 8.14 (d, *J* = 7.2 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.73–7.68 (m, 2 H), 7.60 (t, *J* = 8.4 Hz, 3 H), 7.48 (t, *J* = 7.2 Hz, 1 H), 7.44–7.25 (m, 6 H), 3.99 (s, 3 H), 3.91 (s, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 179.7, 173.6, 159.8, 139.6, 139.0, 138.6, 137.6, 137.1, 132.8, 130.9, 128.8, 125.8, 125.2, 125.0, 124.2, 123.7, 123.6, 122.8, 121.7, 121.6, 116.9, 114.7, 114.3, 111.9, 111.0 , 102.5, 96.6, 79.8, 79.2, 59.8, 34.1, 33.6, 20.8, 14.1. IR (KBr): 3235, 2188, 1650, 1387, 1232, 1125, 1085, 748 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{36}H_{25}N_4O_3$: 561.1921; found: 561.1915.

(*E*)-5-Hydroxy-2-(6-methyl-1*H*-indol-3-yl)-4-[2-(6-methyl-1*H*-indol-3-yl)-2-oxoethylidene]-5-phenyl-4,5-dihydrofuran-3-carbonitrile (3u)

Yield 84%, 214.2 mg; yellow solid; mp 230.1–232.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.64 (s, 1 H), 12.08 (s, 1 H), 9.63 (s, 1 H), 8.62 (s, 1 H), 8.15 (s, 1 H), 8.02 (d, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 6.0 Hz, 2 H), 7.53–7.48 (m, 3 H), 7.41 (s, 1 H), 7.33 (s, 1 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 2.44 (s, 3 H), 2.41 (s, 3 H).^{13}C NMR (100 MHz, DMSO-d_6): δ = 180.1, 173.7, 159.6, 139.1, 136.7, 136.0, 135.9, 134.1, 128.7, 125.5, 125.1, 124.6, 123.8, 123.2, 122.9, 122.1, 121.2, 116.7, 115.6, 114.4, 113.1, 112.3, 103.4, 96.5, 79.3, 56.0, 21.0, 18.7. IR (KBr): 3265, 2205, 1571, 1536, 1503, 1440, 1237, 1018, 765 cm^{-1}. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{32}H_{22}N_4NaO_3$: 533.1584; found: 533.1580.