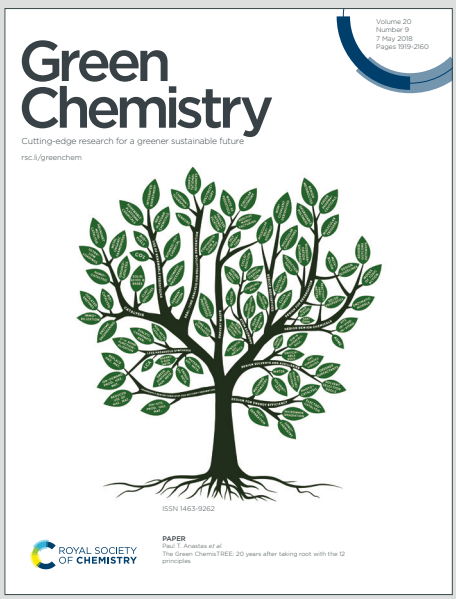
View Article Online
View Journal

Green Chemistry

Cutting-edge research for a greener sustainable future

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Li, X. Dong, N. Zhang, F. Jerome and Y. Gu, *Green Chem.*, 2019, DOI: 10.1039/C9GC02206F.



View Article Online
DOI: 10.1039/C9GC02206F

ARTICLE

Eco-efficient synthesis of 2-quinaldic acids from furfural†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Minghao Li,‡[a] Xiaohan Dong,‡[a] Na Zhang,[a] François Jérôme,*[b] and Yanlong Gu*[a, c]

Quinaldic acids are important fine chemicals. Nowadays, industrial method to synthesize quinaldic acids rely heavily on a three-step process established based on Reissert reaction, which involves however the use of highly toxic potassium cyanide. In this paper, a novel cyclization of aniline with ethyl 4,4-diethoxycrotonate was realized, which offered ethyl quinaldate in good yield. Based on this reaction, an eco-efficient method to prepare quinaldic acid was developed, which involves the following three steps: (i) synthesis of ethyl 4,4-diethoxycrotonate through photooxidation of furfural and a consecutive ring-opening alcoholysis; (ii) cyclization of ethyl 4,4-diethoxycrotonate with aniline, and (iii) hydrolysis of the generated ethyl quinaldate. This new method not only avoids the use of toxic potassium cyanide but also characterized by many salient features of green chemistry, such as the use of bio-based feedstocks, environmentally benign metal-free conditions and good reaction yields.

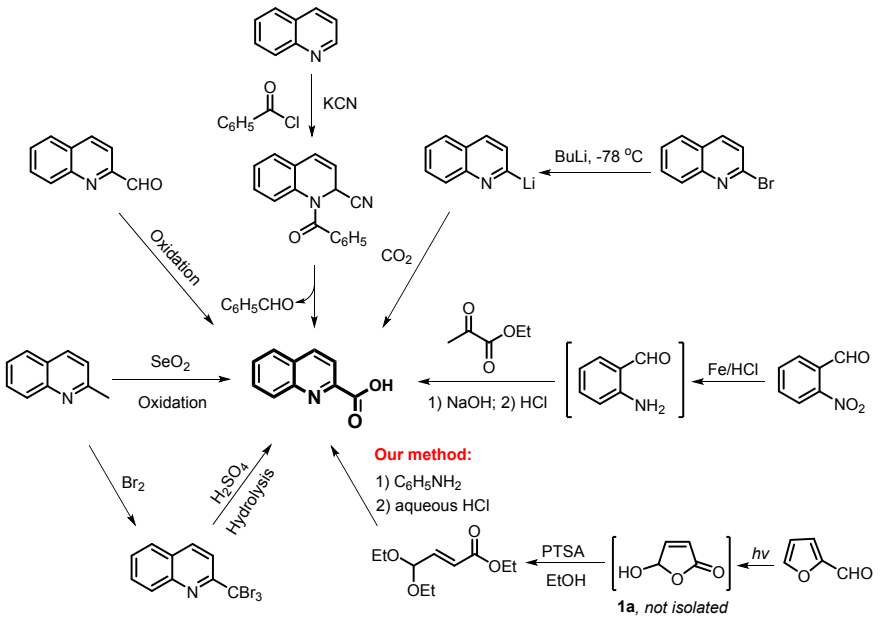
Introduction

Quinolines are ubiquitous structural motifs in many natural products and biologically active pharmaceuticals.[1] The pursuit of synthetic efficiency has stimulated the design and development of new synthetic strategies to construct these heterocycles.[2] Regarding the potential utility, 2-quinaldic acids may be the most attractive products among the different quinoline derivatives. 2-Quinaldic acid, also named as 2-quinolinecarboxylic acid, was widely used as ligand for organometallic chemistry[3] and as synthetic intermediate in pharmaceutical chemistry.[4] It is an important additive for establishing analytic method for determining some metals, such as Cu, Fe, Zn and U.[5] Skeleton of 2-quinolinecarboxylic acid was often involved in some biologically active compounds.[6]

In view of their potential importance, various methods have been developed for the preparation of 2-quinolinecarboxylic acids, which can be catalogized mainly into, as shown in **Scheme 1**, four routes: i) Reissert reaction; quinoline reacted first with benzoyl chloride; and subsequently with potassium cyanide, to give 1-benzoyl-2-cyano-1,2-dihydroquinoline (also known as Reissert compound); the following hydrolysis of this product gives 2-quinaldic acid;[7] Because this method characterized by high selectivity and easy product separation, it was now employed in industry to produce 2-quinaldic acid in large scale;[8] ii) oxidation of 2-quinolinecarboxaldehyde or 2-methylquinoline; because 2-quinolinecarboxaldehyde is rather unstable and expensive, it is only used in laboratory-scale synthesis;[9] direct oxidation of 2-methylquinoline seems to be very attractive; but, the reaction is unfortunately very difficult to carry out selectively because not only of the low reactivity of the methyl group attaching in the quinoline ring, but also of the reversibility of an imine-forming reaction, which resulted in occurrence of a ring-opening of the quinoline ring, damaging further the reaction selectivity;[10] in addition, a stoichiometric amount of toxic SeO_2 was often used as oxidant;[11] a two-step approach established based on using 2-tribromomethylquinoline as intermediate avoided these disadvantages;[12] however, owing to the use of a large amount of bromine, the cost of treating the generated bromide anion-containing waste water is diminishing the real value of this method; iii) carboxylation of 2-quinolinyllithium with CO_2;[13] and iv) one-pot Friedländer quinoline synthesis, *o*-nitroarylcarbaldehyde and alkyl pyruvate were converted, without isolating *o*-aminoarylcarbaldehyde intermediate, into 2-quinaldic acid through a three-step procedure including reduction, condensation and hydrolysis.[14] 2-Quinaldic acid can also be synthesized reportedly from its ester derivatives or 2-cyanoquinoline.[15] All these reported methods are, however, not environmentally benign as it either involves the use of hazardous and expensive reagents, or generates large amount of toxic wastes, which have to be recovered, treated, and disposed. In some cases, the yields and selectivities reported are also far from satisfactory owing to the occurrence of several side reactions. Therefore, an eco-efficient method for

[a] Key Laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan 430074, klgyl@hust.edu.cn
[b] Institut de Chimie des Milieux et Matériaux de Poitiers, Université de Poitiers, ENSIP, 1 rue Marcel Doré, 86073 Poitiers Cedex 9, France, E-mail: francois.jerome@univ-poitiers.fr
[c] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, 730000 Lanzhou, China
† Electronic supplementary information (ESI) available. See DOI: 10.1039/x0xx00000x
‡ Co-first authors.

View Article Online
DOI: 10.1039/C9GC02206F



Scheme 1. Previous methods of synthesizing 2-quinaldic acid.

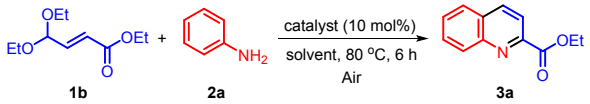
the synthesis of 2-quinaldic acid derivatives is appealingly needed.

Recently, developing new methods for the synthesis of fine chemicals by using renewable bio-based chemicals as starting materials has gained much attention. Furfural is an important bio-based platform molecule that can be obtained in large quantity from pentose containing biomass. Currently, furfural was produced about 300,000 tons per year.[16] Because of the easy availability and great productivity in the world, value-added conversion of furfural emerged as a hot topic of green chemistry in the past decade.[17] However, owing to the lack of multiple reactive sites, it is rather hard to use furfural for fine chemical synthesis. Furfural can be reportedly converted, in almost quantitative yield, to 5-hydroxyfuran-2(5H)-one (a α,β-unsaturated butyrolactone, **1a** through a photooxidation reaction.[18] Hoffmann et al used recently **1a** as precursor to prepare some zwitterionic surfactants.[19] We have long-term interest to develop new organic transformations by using bifunctionalized aldehydes as building blocks for organic synthesis.[20] Based on the structure of **1a**, we envisioned that it may be able to react with aniline in a manner of Doebner-Miller reaction.[21] The reaction, if established, will offer a new and eco-efficient way to synthesize 2-quinaldic acid derivatives. Therefore, we initiated a research program sometime ago. Herein, we disclose the successful outcome of this endeavor in which a congener acetal of **1a** and anilines reacted readily to afford the esters of 2-quinaldic acids in good yield. This reaction enabled us to develop an eco-efficient three-step method for the synthesis of 2-quinaldic acid from furfural.

Results and discussion

We commenced our study from the reaction of **1a** and aniline **2a**. Unfortunately, no desired product was detected under acidic conditions (**Table S1** in supporting information). Considering also **1a** can be easily converted to an ethyl 4,4-diethoxycrotonate **1b**,[22] the reaction of **1b** and aniline **2a** was investigated. In acetonitrile, no reaction occurred in the absence of catalyst (**Table 1**, entry 1). When boron trifluoride

Table 1. Screening of reaction conditions for synthesizing **3a** from **1b** and **2a**.[a]



1b **2a** **3a**

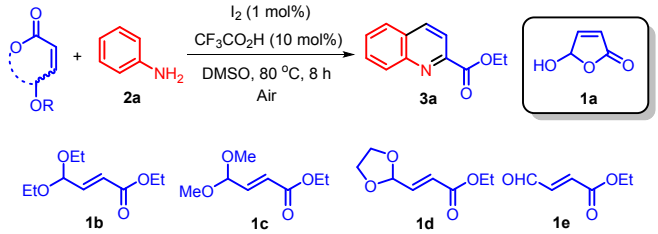
Entry	Catalyst	Solvent	Yield (%)
1	—	MeCN	0
2	$BF_3.Et_2O$	MeCN	15
3	$Sc(OTf)_3$	MeCN	8
4	$FeCl_3$	MeCN	< 5
5	$ZnCl_2$	MeCN	< 5
6	LiBr	MeCN	< 5
7	—	AcOH	66
8[b]	—	Lactic acid	45
9	—	CF_3CO_2H	< 5
10	CF_3CO_2H	DMSO	55
11	—	DMSO	0
12[c]	CF_3CO_2H	DMSO	50
13	CF_3CO_2H/I_2 (1 mol%)	DMSO	62
14	CF_3CO_2H/I_2 (10 mol%)	DMSO	59
15	CF_3CO_2H/NBS (1 mol%)	DMSO	36
16	$CF_3CO_2H/CuBr_2$ (1 mol%)	DMSO	35
17	I_2 (1 mol%)	DMSO	48
18[d]	CF_3CO_2H/I_2 (1 mol%)	DMSO	38
19[e]	CF_3CO_2H/I_2 (1 mol%)	DMSO	40
20[f]	CF_3CO_2H/I_2 (1 mol%)	DMSO	82

[a]: **1b** (0.3 mmol), **2a** (0.3 mmol), solvent (1 mL), 80 °C, 6 h. [b]: 100 °C. [c]: the reaction was performed under oxygen; [d]: 60 °C. [e]: 4 h. [f]: **1b** (0.6 M in 0.5 mL DMSO) was added in 5 hours *via* syringe pump after which the reaction was performed for 3 more hours.

etherate was added, **3a** was isolated after 6 h of reaction at 80 °C in 15% yield (entry 2). Although the yield is rather low, this result is quite promising and demonstrates that it is indeed possible to synthesize **3a** through the model reaction. Other Lewis acids, such as strong ones, $Sc(OTf)_3$ and $FeCl_3$, and weak ones, $ZnCl_2$ and LiBr, were proven, however, ineffective to catalyze this transformation (entries 3 to 6). Intriguingly, by performing this reaction in acetic acid, **3a** can be obtained in 66% yield (entry 7). Replacing acetic acid with lactic acid resulted in a significant yield drop although the reaction was conducted at 100 °C (entry 8). Although using trifluoroacetic acid (TFA) as solvent in this reaction is not successful, a catalytic amount of TFA is sufficient enough to promote the reaction proceed well in dimethyl sulfoxide (DMSO) (entries 9 and 10). No desired product was obtained in the absent of catalyst in DMSO (entry 11). Attempt to increase the yield of **3a** by performing the reaction under oxygen was in vain (entry 12). Interestingly, addition of 1 mol% of iodine seemed beneficial for the reaction (entry 13). However, increasing the amount of iodine didn't further facilitate the reaction (entry 14). This enhancing effect was not observed with some brominating reagents, such as N-bromosuccinimide (NBS) and copper (II) bromide (entries 15 and 16). The reaction with iodine alone proceeded sluggishly (entry 17).[23] Further investigation revealed that the reaction was also affected by temperature and reaction time (entries 18 and 19). The time course of the reaction disclosed that **1b** was the limiting reagent (**Figure S1**). Thus **1b** was added dropwisely via syringe pump. To our delight, the desired product **3a** can be obtained in 82% yield (entry 20).

Then, various **1b**-type aldo-ester molecules were examined in the cyclization reaction with aniline, and the results are listed in **Table 2**. The photooxidation product of furfural, **1a**, reacted hardly with **2a** (entry 1). By using **1c** and **1d** to replace **1b**, the reactions proceeded; however, the yields obtained are slightly inferior as compared with that of **1b**. A parent aldehyde of **1b**, ethyl fumaraldehydate **1e**, was proven amenable in this cyclization, producing **3a** under the identical conditions in 49% yield. All these results indicated that **1b** is the best choice of aldo-ester molecule to synthesize **3a** in the model cyclization. The optimized reaction conditions for construction of ethyl quinaldate are established: (1 mol%), DMSO (1 mL), 80 °C, 8 hours.

Table 2. Synthesis of **3a** through reaction of **2a** with different derivatives of **1a**.[a]



Entry	aldo-ester molecule	Yield (%)
1	**1a**	0
2	**1b**	82
3	**1c**	75
4	**1d**	60
5	**1e**	49

[a]: **2a** (0.3 mmol), aldo-ester molecule (0.3 mmol in 0.5 mL DMSO was added *via* syringe pump in 5 hours), DMSO (0.5 mL), TFA (10 mol%), I_2 (1 mol%), 80 °C, 8 h.

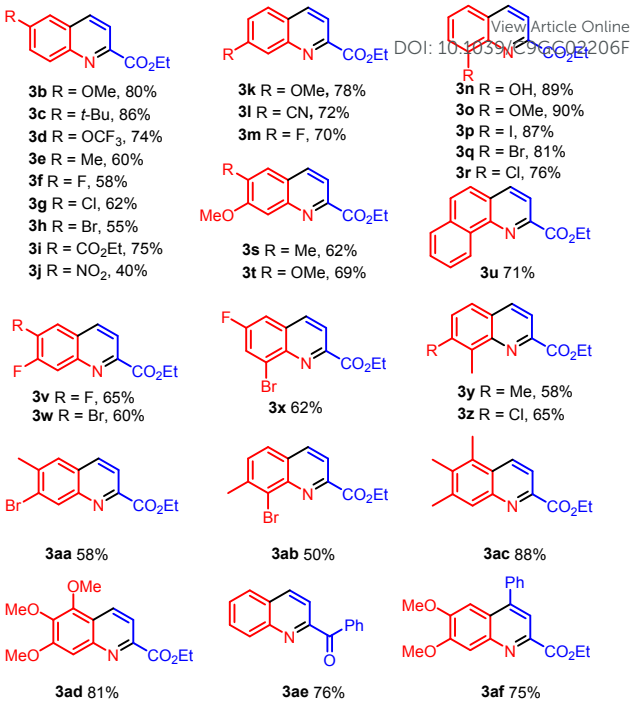
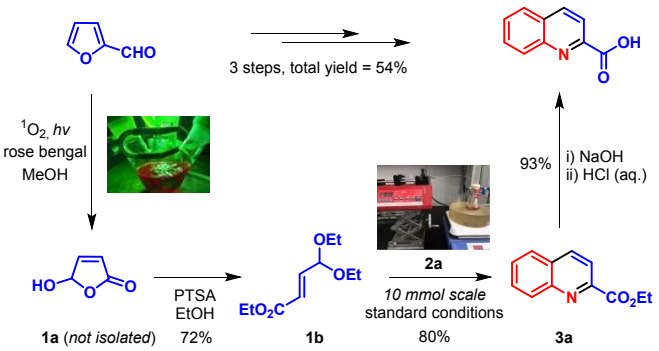


Figure 1. Substrates scope of the model reaction.

With the optimized conditions in hand, the scope of with respect to anilines was explored. As evidenced by the results in **Figure 1**, monosubstituted anilines smoothly reacted with **1b**, producing quinaldate products in good to excellent yields. Generally, the reaction favored electron-rich anilines (**3b** *vs* **3j**; **3k** *vs* **3m**; **3o** *vs* **3q**). In the case of electron-deficient anilines, such as **3j**, the aniline triggered oligomerization of **1b** might happen that resulted in poor yield of the desired reaction.[24] The cyclization of *meta* substituted anilines occurred at the less-sterically hindered site (**3k**–**m**). The ether, halogen, hydroxyl, ester, nitro, and cyano groups were all tolerated in this reaction. The disubstituted anilines were also viable for this transformation, affording corresponding quinaldates in generally good yields. Both electron-rich (**3s**–**u**) and electron-poor (**3v**–**x**) disubstituted anilines readily participated in the reaction and no obvious electronic effect was observed. The effect of simultaneous presence of both electron-withdrawing and electron-donating groups on aniline was also investigated (**3z**, **3aa**, **3ab**). Both the substitutes were well tolerated in the reaction conditions. 3,4,5-Trisubstituted anilines could be employed in this protocol too, giving corresponding quinaldates in excellent yields (**3ac**, **3ad**). The scope of the reaction with respect to **1b** congeners was next explored. It was found that β-keto-α,β-unsaturated acetal performed well in this reaction (**3ae**). The α,β-unsaturated ketone could be directly used in this protocol and furnished **3af** in 75% yield.

View Article Online
DOI: 10.1039/C9GC02206F



Scheme 2. Three steps to synthesize quinolone-2-carboxylic acid from furfural.

To demonstrate the industrialization potential of this method, the reaction was conducted on a 10 mmol scale, and 1.61 g of **3a** was afforded (80% isolated yield). In addition, the synthesis of 2-quinaldic acid from furfural was established in three steps: (i) photooxidation of furfural followed by acid catalysed ring-opening alcoholysis in one pot to generate **1b** in 72% yield; (ii) Doebner-Miller reaction of **1b** with aniline to furnish **3a** in 80% yield; (iii) hydrolysis of the generated ethyl quinaldate to give 2-quinaldic acid in 93% yield. The 2-quinaldic acid was obtained in total 54% yield from furfural (**Scheme 2**).

Mechanistically, in the Doebner-Miller reaction, bio-derived **1b** acted as a 1,3-bis-eletrophile which was further demonstrated as a versatile building block for synthesis of heterocycles. As shown in **Scheme 3**, **1b** reacted readily with some C,O-1,3-bisnucleophiles, such as acetylacetone, ethyl acetoacetate, and 4-hydroxycoumarin to furnish 2*H*-pyrans derivatives (**4a**–**c**). Intriguingly, the 2,3-dihydrobenzofuran **4d** was obtained when **1b** reacted with sesamol, in which **1b** acted as C2 synthons. Instead of aniline, N,O-1,3-bisnucleophiles, 2-mercaptobenzimidazole and 5-amino-3-methyl-1-phenylpyrazole, reacted with 1b **to** furnish substituted 2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (**4d**) and pyrazolo[3,4-*b*]pyridine (**4f**, **4g**), respectively. In addition, 2-aminopyrimidine as a N,N-1,3-bisnucleophile could also be employed to react with **1b** and offered substituted imidazo[1,2-*a*]pyrimidine **4h**,[25] the skeleton of that existed in a numerous bioactive molecules.[26]

Conclusions

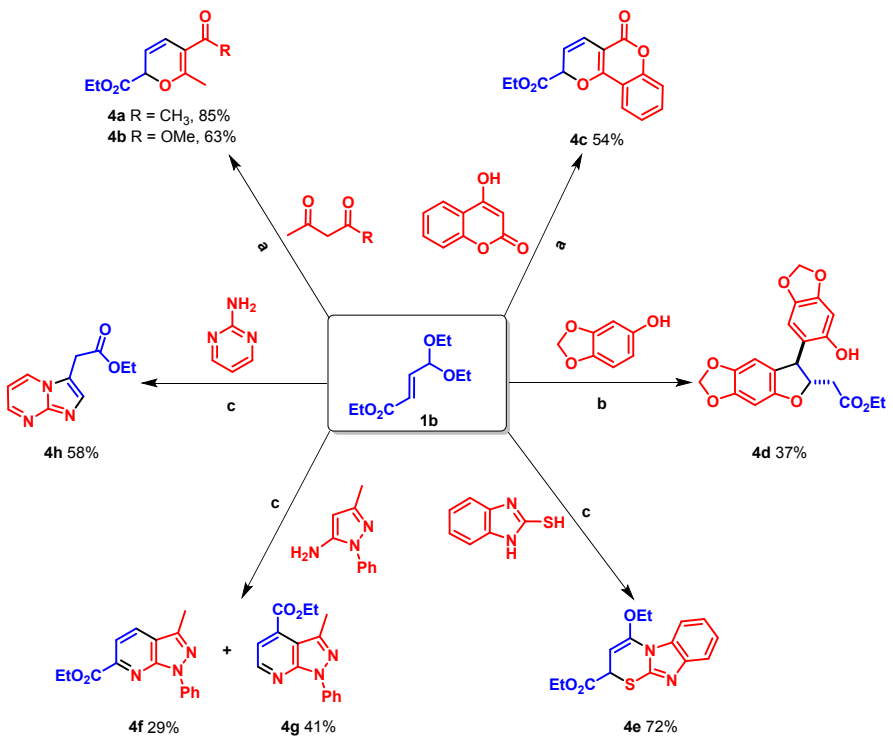
Here we established a three-step process to synthesize quinaldic acid from furfural. This route not only provided a novel way to valorize the bio-based platform molecule into an important fine chemical, but also met many salient features of green chemistry, such as the use of bio-based feedstocks, transitional metal-free conditions, and environmentally benign solvent. Moreover, the ethyl 4,4-dimethoxylcrotonate (**1b**) generated from furfural by photooxidation and a consecutive ring-opening alcoholysis had been demonstrated as a versatile building block for synthesis of heterocycles including quinolone, 2*H*-pyran, dihydrobenzofuran, imidazo[1,2-*a*]pyrimidine, and thiazine derivatives.

Experimental

^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra were recorded on a Bruker AV-400. Chemical shifts are given in parts per million and referenced to the residual solvent signal; all coupling constants are reported in Hz. High-resolution mass spectra (HRMS) were obtained on Brüker Compass Data Analysis 4.0. IR spectra were recorded with a FT-IR Bruker (EQUINOX 55) spectrometer using KBr pellets or neat liquid. Preparative thin-layer chromatography (TLC) and Column chromatography were performed using silica gel GF254 and SiliaFlash®P60, respectively. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification.

Representative procedure for synthesis of 3a

In a 10 mL V-typed flask equipped with a triangle magnetic stirring bar, **2a** (27.9 mg, 0.3 mmol), TFA in 3.0 M DMSO solution (10 μL), I_2 in 0.3 M DMSO solution (10 μL), and DMSO



Scheme 3. The reactions of 1b and bisnucleophiles. a: $MnCl_2{\cdot}4H_2O$ (1.0 equiv.), THF, 60 °C, 8 h; b: $MnCl_2{\cdot}4H_2O$ (1.0 equiv.), CH_3NO_2, 80 °C, 8 h; c: TFA (10 mol%), I_2 (1 mol%), DMSO, 80 °C, 8 h.

View Article Online
DOI: 10.1039/C9GC02305E

(0.5 mL) were mixed together. The mixture was stirred at 80 °C. Then **1b** in 0.6 M DMSO (0.5 mL) was added in 5 hours *via* syringe pump after which the reaction was performed for 3 more hours. Upon completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by preparative TLC (eluting solution: petroleum ether/ethyl acetate = 10/1 (v/v)), yielding the 2*H*-pryrone **3a** in 82% yield (49.5 mg). Similar compounds were prepared following the standard procedure.

Synthesis of quinaldic acid in three steps

Fresh distilled furfural (2.5 mL, 30 mmol), rose bengal (20 mg), and methanol (50 mL) were mixed in a 100 mL round bottom flask. The orange mixture was bubbled with oxygen gas and irradiated by a 450W Ace medium-pressure Hg lamp (quartz filter) for 24 hours. Upon completion, the solution was concentrated in vacuum to afford crude **1a** as an orange paste. Then dried ethanol (60 mL) and PTSA (516.6 mg, 3 mmol) were added inside. The mixture was stirred at 60 °C. After the reaction was completed (monitored by TLC plate), the solution was concentrated in vacuum. The residue was purified *via* vacuum distillation (110 °C at 10 Torr), yielding **1b** in 72% yield (4.37 g, 21.6 mmol). A mixture of **2a** (931.3 mg, 10 mmol), TFA (114.0 mg), I_2 (25.4 mg), and DMSO (15 mL) was stirred at 80 °C. Then **1b** (10 mmol in 15 mL DMSO solution) was added *via* syringe pump in 5 hours after which the reaction was performed for 3 more hours. Upon completion, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (50 mL × 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (SiO_2, petroleum ether to petroleum ether/ethyl acetate = 10/1 (v/v) gradient elution), yielding the **3a** in 80% yield (1.61 g). The **3a** (1.01 g, 5 mmol) was dissolved in a mixed solution of methanol (10.0 mL) and THF (10.0 mL). Then a solution of NaOH (0.6 g, 15 mmol, 3.0 equiv) in H_2O (10 mL) was added and the mixture was stirred for 4 h at room temperature. The solution was then cooled to 0 °C (in an ice and water bath) and acidified with aq. HCl (2.00 N) to pH = 5. The solution was extracted with ethyl acetate (3 x 50 mL) and washed with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to furnish 2-quinaldic acid in 93% yield (0.81 g).

Synthesis of N- or O-containing cyclic compounds from 1b

In a typical experiment, **1b** (60.6 mg, 03. mmol), acetylacetone (30.0 mg, 0.3 mmol), $MnCl_2{\cdot}4H_2O$ (59.4 mg, 0.3 mmol), and THF (2 mL) were combined in a 10 mL V-typed flask equipped with a triangle magnetic stirring bar. The mixture was stirred at 60 °C for 6 hours. After the reaction was completion, the mixture was directly subjected to preparative TLC (eluting solution: petroleum ether/ethyl acetate = 10/1 (v/v)), yielding the 2*H*-pyran **4a** in 85% yield (53.6 mg). Compounds **4b-d** were prepared under identical conditions except that 2.0 equivalents of bisnucleophile and CH_3NO_2 at 80 °C were used for **4d**. The procedure for synthesis of compounds **4e-h** is similar to that of compound **3a** except that the bisnucleophile was added in one pot.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the National Natural Science Foundation of China (2171101076, 21872060) and the Fundamental Research Funds for the Central Universities of China (2016YXZD033, 2019kfyXJJS072) for the financial support. The Cooperative Innovation Center of Hubei Province is also acknowledged.

Notes and references

1 a) K. Kaur, M. Jain, R. P. Reddy, R. Jain, *Eur. J. Med. Chem*. 2010, **45**, 3245–3264; b) J. Barluenga, F. Rodriguez, F. J. Fananas, *Chem. Asian J*. 2009, **4**, 1036–1048; c) J. P. Michael, *Nat. Prod. Rep*. 2008, **25**, 166–187.

2 a) V. V. Kouznetsov, L. Y. V. Mendez, C. M. M. Gomez, *Cur. Org. Chem*. 2005, **9**, 141–161; b) J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. do C. Carreiras, E. Soriano, *Chem. Rev*. 2009, **109**, 2652–2671; c) L.-Y. Xie, Y.-J. Li, J. Qu, Y. Duan, J. Hu, K.-J. Liu, Z. Cao, W.-M. He, *Green Chem.*, 2017, **19**, 5642–5646; d) L.-Y. Xie, T.-G. Fang, J.-X. Tan, B. Zhang, Z. Cao, L.-H. Yang, W.-M. He, *Green Chem.*, 2019, **21**, 3858–3863.

3 a) J. G. Malecki, A. Maron, I. Gryca, A. Mori, T. Suzuki, *Polyhedron* 2013, **62**, 188–202; b) D. Dobrzynska, L. B. Jerzykiewicz, M. Duczmal, A. Wojciechowska, *Polyhedron* 2011, **30**, 2684–2689; c) B. -M. Kukovec, I. Kodrin, Z. Mihalic, Z. Popovic, *Inorg. Chim. Acta* 2011, **378**, 154–162; d) D. Dobrzynska, L. B. Jerzykiewicz, *J. Am. Chem. Soc.* 2004, **126**, 11118–11119; e) P. K. Saikia, P. P. Sarmah, B. J. Borah, L. Saikia, D. K. Dutta, *J. Mol. Catal. A: Chem*. 2016, **412**, 27–33; f) P. P. Sarmah, D. K. Dutta, *J. Mol. Catal. A: Chem*. 2013, **372**, 1–5.

4 P. Bobal, J. Sujan, J. Otevrel, A. Imramovsky, Z. Padelkova, J. Jampilek, *Molecules* 2012, **17**, 1292–1306.

5 a) M. J. Shaw, S. J. Hill, P. Jones, *Anal. Chim. Acta* 1999, **401**, 65–71; b) F. Holmes, W. R. C. Crimmin, *Anal. Chim. Acta* 1956, **15**, 506–507.

6 a) C. Bonini, L. Chiummiento, M. De Bonis, N. Di Blasio, M. Funicello, P. Lupattelli, R. Pandolfo, F. Tramutola, F. Berti, *J. Med. Chem*. 2010, **53**, 1451–1457; b) D. R. St. Laurent, M. H. Serrano-Wu, M. Belema, M. Ding, H. Fang, M. Gao, J. T. Goodrich, R. G. Krause, J. A. Lemm, M. Liu, O. D. Lopez, V. N. Nguyen, P. T. Nower, D. R. O'Boyle II, B. C. Pearce, J. L. Romine, L. S. Valera, J. -H. Valera, Y. -K. Wang, F. Yang, X. Yang, N. A. Meanwell, L. B. Snyder, *J. Med. Chem.* 2014, **57**, 1976–1994.

7 A. Reissert, *Chem. Ber.* 1905, **38**, 1603–1614.

8 a) J. W. Davis, *J. Org. Chem*. 1956, **24**, 1691–1694; b) A. Schwartz, *J. Org. Chem*. 1982, **47**, 2214–2215.

9 a) M. Yoshida, Y. Katagiri, W. -B. Zhu, K. Shishido, *Org. Biomol. Chem*. 2009, **7**, 4062–4066; b) R. H. Dodd, M. Le Hyaric, *Synthesis* 1993, 295–297.

10 a) S. Sakaguchi, A. Shibamoto, Y. Ishii, *Chem. Commun*. 2002, 180–181; b) Y. Tagawa, K. Yamashita, Y. Higuchi, Y. Goto, *Heterocycles,* 2003, **60**, 953–957.

View Article Online
DOI: 10.1039/C9GC02206F

11 J. Jampilek, M. Dolezal, J. Kunes, V. Buchta, L. Silva, K. Kralova, *Med. Chem*. 2005, **1**, 591–599.
12 K. N. Campbell, C. H. Helbing, J. F. Kerwin, *J. Am. Chem. Soc*. 1946, **68**, 1840–1843.
13 J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton, T. F. Jamison, *Angew. Chem. Int. Ed*. 2014, **53**, 8416–8420.
14 A. -H. Li, E. Ahmed, X. Chen, M. Cox, A. P. Crew, H. -Q. Dong, M. Jin, L. Ma, B. Panicker, K. W. Siu, A. G. Steinig, K. M. Stolz, P. A. R. Tavares, B. Volk, Q. Weng, D. Werner, M. J. Mulvihill, *Org. Biomol. Chem*. **2007**, 5, 61–64.
15 a) Q. -D. Zhong, Y. -Z. Xue, H. Yan, X. -Q. Song, R. -G. Zhong, *Bioorg. Med. Chem. Lett.* 2010, **20**, 5532–5535; b) T. D. Tran, N. B. Pham, M. Ekins, J. N. A. Hooper, R. J. Quinn, *Marine Drugs,* 2015, **13**, 4556–4575; c) J. Pajak, E. Lipczynska-Kochany, Z. Eckstein, *Polish J. Chem.* 1982, **56**, 593–599; d) F. Xu, Y. Li, X. Huang, X. Fang, Z. Li, H. Jiang, J. Qiao, W. Chu, Z. Sun, *Adv. Synth. Catal.*, 2019, **361**, 520–525; e) K.W. Rosenmund, E. Struck, *Chem. Ber.*, 1919, **2**, 1749–1756; f) P. S. Fier, *J. Am. Chem. Soc.*, 2017, **139**, 9499–9502.
16 A. S. Mamman, J.-M. Lee, Y.-C. Kim, I. T. Hwang, N.-J. Park, Y. K. Hwang, J.-S. Chang and J.-S. Hwang, Biofuels, *Bioprod. Biorefin*. 2008, **2**, 438–454.
17 a) J.-P. Lange, E. van der Heide, J. van Buijtenen, R. Price, *ChemSusChem*, 2012, **5**, 150–166; b) X. Li, P. Jia, T. Wang, *ACS Catal*., 2016, **6**, 7621–7640; c) R. Mariscal, P. Maireles-Torres, M. Ojeda, I. Sadaba, M. Lopez Granados, *Energy Environ. Sci*. 2016, **9**, 1144–1189.
18 a) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc*. 2003, **125**, 3090–3100; b) J. M. Carney, R. J. Hammer, M. Hulce, C. M. Lomas, D. Miyashiro, *Synthesis* 2012, **44**, 2560–2566; c) J. C. De Jong, F. Van Bolhuis, B. L. Feringa, *Tetrahedron: Asymmetry*, 1991, **2**, 1247–1262.
19 a) A. Gassama, C. Ernenwein and N. Hoffmann, *Green Chem*. 2010, 12, 859–865; b) A. Gassama, C. Ernenwein, A. Youssef, M. Agach, E. Riguet, S. Marinković, B. Estrine, N. Hoffmann, *Green Chem.* 2013, **15**, 1558–1566.
20 a) P. Ravichandiran, B. Lai, Y. Gu, *Chem. Rec*. 2017, **17**, 142–183; b) M. Li, F. Wu, Y. Gu, *Chinese J. Catal.* 2019, **40**, 1135–1140; c) J. Xu, W. Huang, R. Bai, Y. Queneau, F. Jérôme and Y. Gu, *Green Chem.* 2019, **21**, 2061–2069; d) W. Huang, J. Xu, C. Liu, Z. Chen, Y. Gu, *J. Org. Chem.* 2019, **84**, 2941–2950.
21 S. A. Yamashkin, E. A. Oreshkina, *Chem. Heterocycl. Comp*. 2006, **42**, 701–718.
22 S. Rodriguez, A. Vidal, J. J. Monroig, F. V. Gonzalez, *Tetrahedron Lett*. 2004, **45**, 5359–5361.
23 A proposed mechanism for the I_2 catalysed Doebner-Miller Reaction was depicted in Scheme S1 in the supporting information.
24 B. Massoumi, M. Abdollahi, S. J. Shabestari, A. A. Entezami, *J. Appl. Polym. Sci.* 2013, **128**, 47–53.
25 The reaction pathway for synthesis of imidazo[1,2-*a*]pyrimidine 4h from 2-aminopyrimidine and 1b was proposed in Scheme S2 in the supporting information.
26 For selected examples see: a) W.R. Tully, C.R. Gardner, R.J. Gillespie, R. Westwood, *J. Med. Chem.*, 1991, **34**, 2060–2067; b) W.P. Blackaby, J.R. Atack, F. Bromidge, J.L. Castro, S.C. Goodacre, D.J. Hallett, R.T. Lewis, G.R. Marshall, A. Pike, A.J. Smith, L.J. Street, D.F.D. Tattersall, K.A. Wafford, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1175–1179; c) T. Juspin, M. Laget, T. Terme, N. Azas, P. Vanelle, *Eur. J. Med. Chem.*, 2010, **45**, 840–845; d) A. Marwaha, J. White, F. El Mazouni, S.A. Creason, S. Kokkonda, F.S. Buckner, S.A. Charman, M.A. Phillips, P.K. Rathod, *J. Med. Chem.*, 2012, **55**, 7425–7436.