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ZnCl₂-promoted domino reaction of 2-hydroxybenzoxazinones with ketones for synthesis of 1,3-benzoxazin-4-ones†

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A ZnCl₂-promoted synthesis of 1,3-benzoxazin-4-one from 2-hydroxybenzoxazinones and ketones was developed. This method displays facile access to a diverse range of substituted 1,3-benzoxazin-4-ones in good yields. This synthetic protocol has advantages: (i) easy availability of starting material; (ii) strong corrosive acid-free condition; (iii) high yield.

Introduction

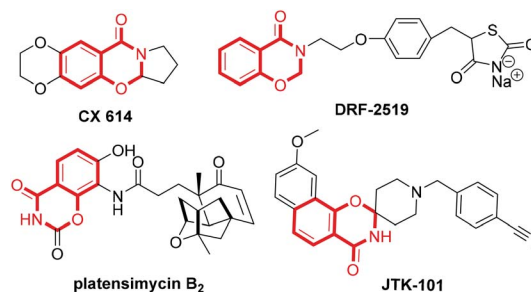
Synthesis of fused nitrogenous heterocyclic compounds is the major “workhorse” for synthetic chemists because of their wide applications in pharmaceutical and materials chemistry. Among them, 1,3-benzoxazin-4-one derivatives have been assigned as synthetic auxiliaries in drug discovery owing to their well-documented medicinal properties.¹ For example, the 1,3-benzoxazin-4-one moiety is found in several biologically active and pharmaceutically relevant scaffolds (Scheme 1), such as CX-614,² DRF-2519,³ platensimycin B₂ (ref. 4) and JTK-101.⁵ The traditional synthetic approach towards 1,3-benzoxazin-4-ones employs the condensation of suitably substituted salicylamides with aldehydes or ketones,⁶ or derivatives of *N*-acylated anthranilic acid.⁷ These procedures suffer from harsh reaction condition, low yield, as well as use of a strong acid as a catalyst. In 2011, Coates and colleagues⁸ reported a cobalt-catalyzed hydroformylation of dihydrooxazines for the facile construction of CX-614 and related substances. In 2014, Maiti and co-workers^{7b} developed a (sp³) C–O bond formation through copper-catalyzed intramolecular dehydrogenative coupling for assembling substituted oxazinones. However, both strategies use customized reagents as the starting material, and are more applicable to the synthesis of 1,3-benzoxazin-4-ones with specific structures. Therefore, developing economical and environmentally benign protocols with readily available starting

materials and catalyst for the general preparation of 1,3-benzoxazin-4-one is highly valuable.

o-Aminonitrile is a versatile synthon and has been applied widely to the construction of important nitrogen-bearing heterocyclic compounds.⁹ The domino reaction is a convenient method for organic synthesis.¹⁰ During the past decade, we have synthesized many fused heterocycles employing the modified Friedländer cyclocondensation of *o*-aminonitriles with carbonyl compounds (PDF conversion).¹¹ Analogously, we speculated that 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones would be provided by the similar cyclocondensation of salicylonitrile instead of 2-aminobenzonitrile condensed with carbonyl compounds (Scheme 2). There is no report on the synthesis of 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones *via* heterocyclic condensation of 2-hydroxybenzoxazinone with carbonyl compounds. Herein we report these results.

Results and discussion

Fortunately, the expected 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones were obtained by the condensation of 2-hydroxybenzoxazinone **1a** with cyclohexanone **2a** in the presence of a Lewis acid in boiling solvent. Then, the reaction of **1a** and **2a** was chosen as the



Scheme 1 Examples of biologically active benzoxazinones.

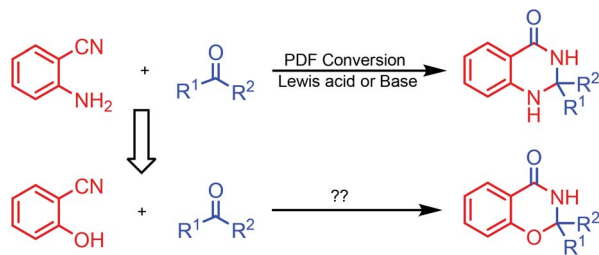
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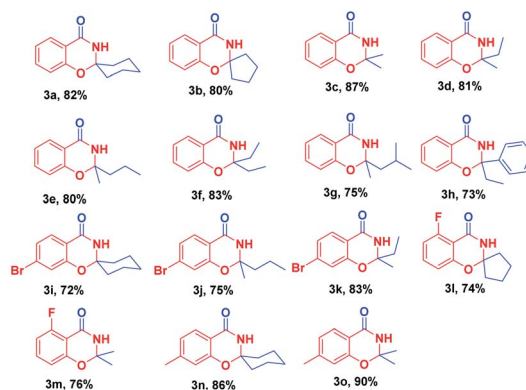




Scheme 2 Design synthesis of 4H-1,3-benzoxazin-4-ones.

model substrate to optimize the conditions (Table 1). Various Lewis acids and protonic acids were evaluated for the reaction, and ZnCl_2 was identified as the most efficient accelerant for the reaction in terms of highest yield (Table 1, entry 2). TsOH was also an efficient accelerant, but the reaction gave product **3a** with a lower yield (Table 1, entry 1). However, no reaction was observed under the other tested accelerants (FeCl_3 , TiCl_4 , AlCl_3 , PPA , T_3P) (Table 1, entries 3–7). In addition, the effect of solvents was investigated, and cyclohexanone itself was the best choice for the ZnCl_2 -promoted cyclization of 2-hydroxybenzonitrile with cyclohexanone (Table 1, entries 2, 8–11). Thus, the optimal conditions for the formation of **3a** were developed (Table 1, entry 2).

With optimized reaction conditions in hand, the substrate scope of this ZnCl_2 -promoted cyclization reaction was investigated. As presented in Table 2, a series of ketones ranging from aliphatic ketones to aromatic ketones were allowed to react with 2-hydroxybenzonitrile under the reaction condition established. The method was successful for all cyclic and branched ketone substrates tested (Table 2, **3a–3g**). For example, spiro-heterocyclic benzo[*e*][1,3]oxazin-4(3*H*)-ones were obtained from the

Table 2 Scope of substrates^{a,b}

^a Reaction conditions: **1** (1.0 mmol), ZnCl_2 (1.1 mmol), corresponding ketones as solvent (5.0 ml), 100 °C, 6 h, under an air atmosphere. Isolated yield. ^b Toluene (5.0 ml) as solvent for **3c**, **3d**, **3m** and **3o**.

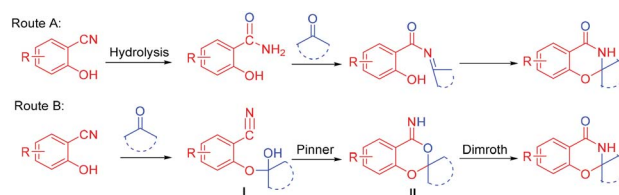
condensation of **1a** with cyclic ketones (Table 2, **3a**, **3b**). Then, we investigated the reaction of **1a** with a range of linear aliphatic ketones (Table 2, **3c–3g**): all the aliphatic ketones tested participated in this reaction smoothly with moderate yield of **3**. Therefore, we concluded that a branched chain did not have a significant effect on this reaction. Even poorly reactive aromatic ketones (e.g., propiophenone) were cyclized to give a good yield of the fused ring system **3h** (Table 2, **3h**). This ZnCl_2 -catalyzed cyclization reaction could tolerate many functional groups, such as the C–Br bond, C–F bond, and the methyl group in aryl *o*-hydroxynitrile, to afford good-to-excellent yields of the corresponding 2,3-dihydro-4H-1,3-benzoxazin-4-ones.

The two possible mechanisms of this reaction are shown in Scheme 3. In route A, the nitrile group of *o*-hydroxybenzonitrile was hydrolyzed first,^{6b} and the corresponding skeleton was prepared from salicylamide. However, only 42% of the cyclization product was obtained by the reaction of salicylamide and cyclohexanone under optimal conditions, which was only half of the yield of the direct cyclization of 2-hydroxybenzonitrile and cyclohexanone. Second, when the reaction system was strictly controlled without water, salicylamide was not detected during the reaction. Hence, route A was not suitable. Upon referring to the literature,^{9e,11,12} we propose that the reaction proceeds through a tandem intramolecular Pinner–Dimroth rearrangement pathway (route B). First, the key intermediate **I** is formed by addition of the hydroxyl group of the salicylonitrile onto the carbonyl of the ketones. Subsequent intramolecular nucleophilic attack of the hydroxyl group to the nitrile group *via*

Table 1 Optimization of reaction conditions^a

Entry	Acid	Solvent	Temp (°C)	Yield ^b (%)
1	TsOH	Cyclohexanone	Reflux	60
2	ZnCl_2	Cyclohexanone	Reflux	82 (72, ^c 83 ^d)
3	FeCl_3	Cyclohexanone	Reflux	0
4	TiCl_4	Cyclohexanone	Reflux	0
5	AlCl_3	Cyclohexanone	Reflux	0
6	PPA^e	Cyclohexanone	Reflux	Trace
7	T_3P^f	Cyclohexanone	Reflux	Trace
8	ZnCl_2	Dioxane	Reflux	61
9	ZnCl_2	DMF	120	53
10	ZnCl_2	NMP	120	55
11	ZnCl_2	Toluene	Reflux	70

^a Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), accelerant (1.1 mmol), solvent (5.0 ml), 100 °C, 6 h, under an air atmosphere. ^b Isolated yield. ^c Time: 4 h. ^d Time: 12 h. ^e Polyphosphoric acid. ^f Tricyclic acid propionate.



Scheme 3 Possible reaction mechanisms.



an intramolecular Pinner reaction¹³ results in the cyclized benzo[*d*][1,3]dioxin-4-imine **II**, which subsequently rearranges (Dimroth rearrangement¹⁴) to afford the final product.

The chemical structures of target compounds **3** were characterized fully by spectroscopy (IR, ¹H NMR, ¹³C NMR, and MS-ESI). A single crystal of **3a**, suitable for X-ray crystallography, was obtained by slow evaporation of THF. The structure clearly showed that **3a** was built-up from two fused six-membered rings and one six-membered ring linked through a spiro C atom, and the cyclohexane ring had an “envelope” conformation. In the crystal, two adjacent molecules were linked by double intermolecular N–H⋯O (2.059) hydrogen bonds and further assembled into a two-dimensional network interacted by van der Waals forces and C–H⋯π interactions (Fig. 1a).¹⁴ In addition, HSQC (Fig. 1b) and ¹H,¹H-COSY NMR (Fig. 1c) experiments were undertaken, and all the signals could be assigned unambiguously.

Experimental

General information

Unless noted otherwise, all chemicals were purchased from commercial suppliers and used without further purification. All experiments were monitored by thin-layer chromatography (TLC) and visualized under UV light (254 nm). Column chromatography was undertaken on SiliCycle silica gel (200–300 mesh). Melting points were determined using melting-point apparatus (XT4 microscope). IR spectra was recorded on a FT-IR spectrophotometer (PerkinElmer) with KBr pellets. ¹H and

¹³C NMR spectra were recorded at a mercury-plus 400 spectrometer (Varian) in DMSO-*d*₆ with TMS as the internal standard. ESI-MS was carried out on an APEXII FT-ICR (Bruker) using ESI. HR-MS was recorded on an APEXIV FT-ICR mass spectrometer (Bruker).

General experimental procedure for the synthesis of 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones

A sample vial (25 ml) equipped with a magnetic stirring bar was charged with 2-hydroxybenzoxazinones (1.0 mmol), ZnCl₂ (1.1 mmol), and 5 ml of the corresponding ketone (toluene as the solvent for acetone and butanone). The reaction proceeded under an air atmosphere and was heated for 6 h at 120 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate. The organic layers were combined, dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography or recrystallization using petroleum ether/EtOAc to provide the analytically pure product **3**.

Spiro[benzo[*e*][1,3]oxazine-2,1'-cyclohexan]-4(3*H*)-one (**3a**)

White solid, m.p. 201–203 °C; IR (KBr, ν, cm⁻¹): 3192, 3078, 2938, 2861, 1670, 1607, 1467, 770; ¹H-NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 8.65 (s, 1H), 7.75–7.73 (m, 1H), 7.52–7.48 (m, 1H), 7.10–7.06 (m, 1H), 7.01–6.99 (q, *J* = 8.8 Hz, 1H), 1.99 (t, *J* = 11.2 Hz, 2H), 1.63–1.53 (m, 7H), 1.24 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 161.56, 155.47, 134.79, 127.48, 122.12, 118.39, 117.37, 88.02, 35.86 (2C), 24.63, 21.89 (2C); ESI-MS (*m/z*) = 218.4 ([M + H]⁺).

Spiro[benzo[*e*][1,3]oxazine-2,1'-cyclopentan]-4(3*H*)-one (**3b**)

Light-yellow solid, m.p. 133–136 °C; IR (KBr, ν, cm⁻¹): 3192, 3078, 2938, 2861, 1670, 1607, 1467, 770; ¹H-NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 8.75 (s, 1H), 7.76–7.74 (q, *J* = 8.8 Hz, 1H), 7.51–7.47 (m, 1H), 7.09 (t, *J* = 14.8 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 2.07–2.02 (m, 2H), 1.86–1.79 (m, 2H), 1.75–1.71 (q, *J* = 16.4 Hz, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 162.22, 156.27, 134.73, 127.64, 122.23, 118.40, 117.47, 97.94, 37.90 (2C), 22.83 (2C); ESI-MS (*m/z*) = 204.1 ([M + H]⁺).

2,2-Dimethyl-2,3-dihydro-4*H*-benzo[*e*][1,3]oxazin-4-one (**3c**)

White solid, m.p. 138–140 °C; IR (KBr, ν, cm⁻¹): 3183, 3071, 2907, 1679, 1614, 1470, 754; ¹H-NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 8.65 (s, 1H), 7.76–7.74 (q, *J* = 9.2 Hz, 1H), 7.52–7.48 (m, 1H), 7.10–7.06 (m, 1H), 6.98–6.95 (q, *J* = 8.8 Hz, 1H), 1.53 (s, 6H); ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm): 161.55, 155.90, 134.89, 127.50, 122.09, 117.66, 117.30, 87.87, 27.69 (2C); ESI-MS (*m/z*) = 178.4 ([M + H]⁺).

2-Ethyl-2-methyl-2,3-dihydro-4*H*-benzo[*e*][1,3]oxazin-4-one (**3d**)

Light-yellow solid, m.p. 127–128 °C; IR (KBr, ν, cm⁻¹): 3180, 3062, 2970, 2933, 1671, 1614, 1470; ¹H-NMR (400 MHz, DMSO-*d*₆) (δ, ppm): 8.60 (s, 1H), 7.76–7.37 (m, 1H), 7.51–7.46 (m, 1H), 7.09–7.05 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 1.82–1.76 (q, *J* = 21.6 Hz, 2H), 1.47

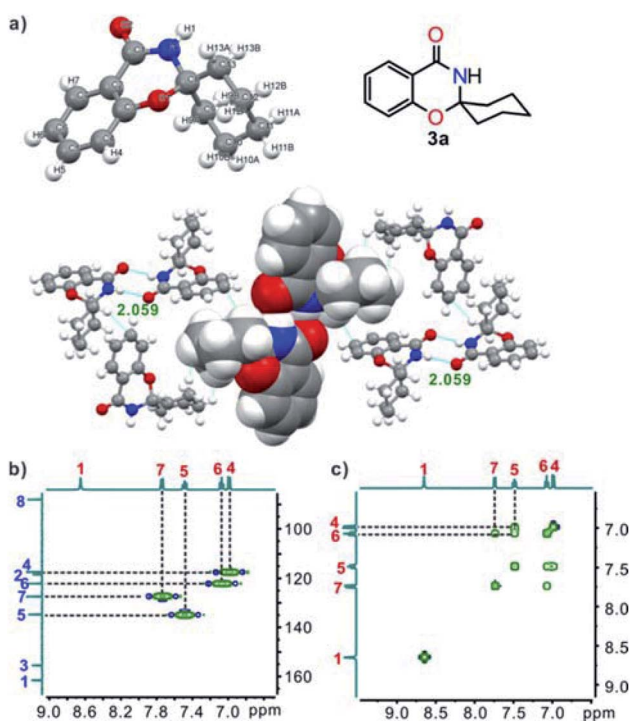


Fig. 1 (a) X-ray single-crystal structure and two-dimensional network of **3a** (O, red; N, blue; C, gray; H, white); (b) partial HSQC spectrum of **3a**; (c) partial ¹H–¹H COSY spectrum of **3a**.



(s, 3H), 0.91 (t, $J = 14.8$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.61, 155.92, 134.83, 127.42, 121.98, 117.76, 117.26, 89.92, 32.63, 25.44, 8.37; ESI-MS (m/z) = 192.5 ($[\text{M} + \text{H}]^+$).

2-Methyl-2-propyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3e)

Light-yellow solid, m.p. 72–75 °C; IR (KBr, v, cm^{-1}): 3194, 3158, 3081, 2989, 2959, 2861, 1676, 1614, 1469, 757; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.63 (s, 1H), 7.76–7.73 (q, $J = 12.0$ Hz, 1H), 7.50–7.46 (m, 1H), 7.06 (t, $J = 14.8$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 1.77–1.72 (m, 2H), 1.48 (s, 3H), 1.44–1.38 (m, 2H), 0.85 (t, $J = 13.6$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.54, 155.90, 134.83, 127.42, 121.96, 117.72, 117.24, 89.63, 42.01, 25.91, 17.01, 14.33; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_2$ 206.1181, found 206.1176.

2,2-Diethyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3f)

White solid, m.p. 95–97 °C; IR (KBr, v, cm^{-1}): 3192, 3078, 2938, 2861, 1670, 1607, 1467, 770; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.56 (s, 1H), 7.74 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 18.0$ Hz, 1H), 7.06–7.01 (q, $J = 22.0$ Hz, 1H), 6.94 (t, $J = 17.6$ Hz, 1H), 1.80–1.73 (m, 4H), 0.89 (t, $J = 14.8$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.72, 156.10, 134.77, 127.34, 121.79, 117.68, 117.16, 92.01, 30.49 (2C), 8.03 (2C); ESI-MS (m/z) = 206.1 ($[\text{M} + \text{H}]^+$).

2-Isobutyl-2-methyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3g)

White solid, m.p. 77–79 °C; IR (KBr, v, cm^{-1}): 3194, 3158, 3081, 2939, 2959, 1676, 1614, 1469, 757; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.59 (s, 1H), 7.76–7.74 (q, $J = 9.2$ Hz, 1H), 7.51–7.46 (m, 1H), 7.08–7.04 (m, 1H), 6.94–6.92 (q, $J = 8.8$ Hz, 1H), 1.91–1.84 (m, 1H), 1.75–1.65 (m, 2H), 1.51 (s, 1H), 0.92–0.89 (q, $J = 10.8$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.51, 155.78, 134.84, 127.39, 121.95, 117.60, 117.32, 90.02, 47.77, 26.38, 24.45, 24.15, 23.91; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2$ 220.13321, found 220.13287.

2-Ethyl-2-phenyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3h)

Light-yellow solid, m.p. 135–137 °C; IR (KBr, v, cm^{-1}): 3182, 3064, 2987, 2932, 1676, 1614, 1469, 754; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 9.38 (s, 1H), 7.61–7.59 (q, $J = 9.2$ Hz, 1H), 7.45–7.41 (m, 3H), 7.31 (t, $J = 14.8$ Hz, 2H), 7.23 (t, $J = 14.4$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 6.97 (t, $J = 14.8$ Hz, 1H), 2.04–1.92 (m, 2H), 1.00 (t, $J = 14.8$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 162.69, 156.49, 143.96, 134.88, 128.66 (2C), 128.46, 127.45, 126.37 (2C), 122.26, 118.54, 117.74, 91.96, 35.59, 8.39; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{16}\text{H}_{16}\text{NO}_2$ 254.11756, found 254.11832.

7-Bromospiro[benzo[e][1,3]oxazine-2,1'-cyclohexan]-4(3H)-one (3i)

White solid, m.p. 187–189 °C; IR (KBr, v, cm^{-1}): 3182, 3070, 2939, 2859, 1673, 1603, 1434; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.79 (s, 1H), 7.67–7.65 (q, $J = 8.4$ Hz, 1H), 7.28 (m, 2H), 1.98 (t, $J = 12.0$ Hz, 2H), 1.64–1.58 (m, 7H), 1.24 (s, 1H); ^{13}C NMR

(100 MHz, DMSO- d_6) (δ , ppm): 160.86, 156.20, 129.28, 127.55, 125.42, 120.32, 117.66, 89.00, 35.88 (2C), 24.56, 21.84 (2C); HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{13}\text{H}_{15}\text{BrNO}_2$ 296.02776, found 296.02807.

7-Bromo-2-methyl-2-propyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3j)

Light-yellow solid, m.p. 101–103 °C; IR (KBr, v, cm^{-1}): 3180, 3158, 3068, 2959, 2939, 1685, 1601, 1430; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.79 (s, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.29–7.24 (m, 2H), 1.78–1.73 (m, 2H), 1.49 (s, 3H), 1.43–1.37 (q, $J = 22.0$ Hz, 2H), 0.86 (t, $J = 14.8$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 160.84, 156.61, 129.25, 127.60, 125.28, 120.14, 116.97, 90.59, 42.12, 25.92, 16.96, 14.29; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{BrNO}_2$ 284.02776, found 284.02807.

7-Bromo-2,2-diethyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3k)

White solid, m.p. 125–130 °C; IR (KBr, v, cm^{-1}): 3176, 3066, 2976, 2936, 1685, 1601, 1433; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.75 (s, 1H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.28–7.25 (m, 2H), 1.81–1.74 (m, 4H), 0.89 (t, $J = 14.8$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.02, 156.81, 129.17, 127.58, 125.13, 120.08, 116.91, 93.01, 30.54 (2C), 8.01 (2C); HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{BrNO}_2$ 284.02777, found 284.02807.

5-Fluorospiro[benzo[e][1,3]oxazine-2,1'-cyclopentan]-4(3H)-one (3l)

Yellow oil; IR (KBr, v, cm^{-1}): 3192, 3087, 2975, 2919, 1683, 1623; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.88 (s, 1H), 7.52–7.46 (m, 1H), 6.91–6.78 (m, 2H), 2.07–1.99 (m, 2H), 1.88–1.80 (m, 2H), 1.74–1.69 (m, 4H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.66 (d, $J = 258.0$ Hz), 159.45 (d, $J = 2.3$ Hz), 157.73 (d, $J = 3.5$ Hz), 135.24 (d, $J = 11.2$ Hz), 113.76 (d, $J = 3.6$ Hz), 110.36 (d, $J = 21.0$ Hz), 107.82 (d, $J = 9.6$ Hz), 98.09, 37.61 (2C), 22.80 (2C); HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{12}\text{H}_{13}\text{FNO}_2$ 222.09248, found 222.09243.

5-Fluoro-2,2-dimethyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3m)

White solid, m.p. 145–148 °C; IR (KBr, v, cm^{-1}): 3200, 3083, 2931, 1683, 1622, 1047; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.74 (s, 1H), 7.53–7.47 (m, 1H), 6.90–6.82 (m, 2H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.64 (d, $J = 129.1$ Hz), 158.80 (d, $J = 2.4$ Hz), 157.37 (d, $J = 3.5$ Hz), 135.36 (d, $J = 11.3$ Hz), 113.58 (d, $J = 3.6$ Hz), 110.11 (d, $J = 21.0$ Hz), 107.14 (d, $J = 9.4$ Hz), 88.07, 27.38 (2C); HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{10}\text{H}_{11}\text{FNO}_2$ 196.07683, found 196.07671.

7-Methylspiro[benzo[e][1,3]oxazine-2,1'-cyclohexan]-4(3H)-one (3n)

White solid, m.p. 200–202 °C; IR (KBr, v, cm^{-1}): 3186, 3075, 2936, 2919, 1678, 1621; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.52 (s, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.82 (s, 1H), 2.31 (s, 3H), 1.98 (t, $J = 11.6$ Hz, 2H), 1.62–1.52 (m, 7H),



1.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.65, 155.47, 145.37, 127.34, 123.06, 117.52, 115.83, 87.99, 35.88 (2C), 24.66, 21.92 (2C), 21.68; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ 232.13321, found 232.13344.

2,2,7-Trimethyl-2,3-dihydro-4H-benzo[e][1,3]oxazin-4-one (3o)

White solid, m.p. 164–166 °C; IR (KBr, ν , cm^{-1}): 3181, 3071, 2990, 2912, 1677, 1618; ^1H -NMR (400 MHz, DMSO- d_6) (δ , ppm): 8.53 (s, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.78 (s, 1H), 2.31 (s, 3H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, DMSO- d_6) (δ , ppm): 161.67, 155.92, 145.45, 127.37, 123.04, 117.43, 115.13, 87.83, 27.69 (2C), 21.69; HR-ESI ($[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_2$ 192.10191, found 192.10208.

Conclusions

We demonstrated a new ZnCl_2 -promoted domino approach for the synthesis of 1,3-benzoxazin-4-one derivatives *via* the cyclization of 2-hydroxybenzoxanitriles and ketones. We have applied for a patent in China.¹⁵ Such a novel methodology using inexpensive and commercially available reagents and Lewis acid provides convenient and highly efficient access to 1,3-benzoxazin-4-ones. The methodology has several notable advantages: operational simplicity, mild conditions, time efficiency and easy workup. This synthetic method offers a complementary strategy for construction of 1,3-benzoxazin-4-ones.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) D. A. Griffith, R. L. Dow, K. Huard, D. J. Edmonds, S. W. Bagley, J. Polivkova, D. Zeng, C. N. Garcia-Irizarry, J. A. Southers, W. Esler, P. Amor, K. Loomis, K. McPherson, K. B. Bahnck, C. Preville, T. Banks, D. E. Moore, A. M. Mathiowetz, E. Menhaji-Klotz, A. C. Smith, S. D. Doran, D. A. Beebe and M. F. Dunn, *J. Med. Chem.*, 2013, **56**, 7110–7119; (b) G. R. Madhavan, R. Chakrabarti, K. A. Reddy, B. M. Rajesh, V. Balraju, P. B. Rao, R. Rajagopalan and J. Iqbal, *Bioorg. Med. Chem.*, 2006, **14**, 584–591; (c) K. D. Wellington, R. C. Cambie, P. S. Rutledge and P. R. Bergquist, *J. Nat. Prod.*, 2000, **63**, 79–85.
- (a) D. Eleni, R. Claire-Marie, G. Fabien, S. Michael and G. Pierre, *Brain Res.*, 2003, **970**, 221–225; (b) C. A. Amy, K. Markus, R. Gary and L. Gary, *Mol. Pharmacol.*, 2000, **58**, 802–813; (c) R. Mueller, Y.-X. Li, A. Hampson, S. Zhong, C. Harris, C. Marrs, S. Rachwal, J. Ulas, L. Nielsson and G. Rogers, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3923–3924; (d) R. Mueller, S. Rachwal, M. E. Tedder, Y.-X. Li, S. Zhong, A. Hampson, J. Ulas, M. Varney, L. Nielsson and G. Rogers, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3927–3930.
- G. R. Madhavan, R. Chakrabarti, K. A. Reddy, B. M. Rajesh, V. Balraju, P. B. Rao, R. Rajagopalan and J. Iqbal, *Bioorg. Med. Chem.*, 2006, **14**, 584–591.
- (a) C. Zhang, J. Ondeyka, K. Herath, H. Jayasuriya, Z. Guan, D. L. Zink, L. Dietrich, B. Burgess, S. N. Ha, J. Wang and S. B. Singh, *J. Nat. Prod.*, 2011, **74**, 329–340; (b) M. Saleem, H. Hussain, I. Ahmed, T. V. Ree and K. Krohn, *Nat. Prod. Rep.*, 2011, **28**, 1534–1579.
- (a) M. Shi, X. Wang, M. Okamoto, S. Takao and M. Baba, *Antiviral Res.*, 2009, **83**, 201–204; (b) X. Wang, K. Yamataka, M. Okamoto, S. Ikeda and M. Baba, *Antiviral Chem. Chemother.*, 2007, **18**, 201–211.
- (a) B. W. Horro and H. Zaugg, *J. Am. Chem. Soc.*, 1950, **72**, 721–724; (b) R. B. Gammill, *J. Org. Chem.*, 1981, **46**, 3340–3342; (c) S. D. Sharma and V. Kaur, *Synthesis*, 1989, **9**, 677–680; (d) S. H. Kim, Y. M. Kim and J. N. Kim, *Bull. Korean Chem. Soc.*, 2010, **31**, 2351–2356; (e) S. Hussain, S. Jadhav, M. Rai and M. Farooqui, *Rasayan J. Chem.*, 2012, **5**, 148–151.
- (a) A. N. Kandale, R. Ohlyan and G. Kumar, *Int. J. Pharm. Pharm. Sci.*, 2014, **6**, 68–71; (b) A. Modak, U. Dutta, R. Kancharla, S. Maity, M. Bhadra, S. M. Mobin and D. Maiti, *Org. Lett.*, 2014, **16**, 2602–2605.
- M. Mulzer and G. W. Coates, *Org. Lett.*, 2011, **13**, 1426–1428.
- (a) K. B. Rasal and G. D. Yadav, *Org. Process Res. Dev.*, 2016, **20**, 2067–2073; (b) M. Ekiza, A. Tutarb and S. Ökten, *Tetrahedron*, 2016, **72**, 5323–5330; (c) W. Li, N. Yang and Y. Lyu, *Org. Chem. Front.*, 2016, **3**, 823–835; (d) F. Tamaddon and F. Pouramini, *Synlett*, 2014, **25**, 1127–1131; (e) X.-F. Wu, S. Oschatz, A. Block, A. Spannenberg and P. Langer, *Org. Biomol. Chem.*, 2014, **12**, 1865–1870; (f) H. Q. Li, L. He, H. Neumann, M. Bellera and X.-F. Wu, *Green Chem.*, 2014, **16**, 1336–1343; (g) X.-L. Pang, C. Chen, X. Su, M. Li and L.-R. Wen, *Org. Lett.*, 2014, **16**, 6228–6231; (h) J. Han, L. Cao, L. Bian, J. Chen, H. Deng, M. Shao, Z. Jin, H. Zhang and W. Cao, *Adv. Synth. Catal.*, 2013, **355**, 1345–1350.
- (a) Y. Wu, J. Y. Chen, J. Ning, X. Jiang, J. Deng, Y. Deng, R. Xu and W. M. He, *Green Chem.*, 2021, **23**, 3950–3954; (b) Q. W. Gui, F. Teng, S. N. Ying, Y. Liu, T. Guo, J. X. Tang, J. Y. Chen, Z. Cao and W. M. He, *Chin. Chem. Lett.*, 2020, **31**, 3241–3244; (c) Q. W. Gui, B. B. Wang, S. Zhu, F. L. Li, M. X. Zhu, M. Yi, J. L. Yu, Z. L. Wu and W. M. He, *Green Chem.*, 2021, **23**, 4430–4434; (d) W. B. He, L. Q. Gao, X. J. Chen, Z. L. Wu, Y. Huang, Z. Cao, X. H. Xu and W. M. He, *Chin. Chem. Lett.*, 2020, **31**, 1895–1898.
- (a) S. L. Ma, J. R. Li, Y. J. Sun, J. M. Zhao, X. F. Zhao, X. Q. Yang, L. J. Zhang, L. J. Wang and Z. M. Zhou, *Tetrahedron*, 2006, **62**, 7999–8005; (b) J. R. Li, L. J. Zhang, D. X. Shi, Q. Li, D. Wang, C. Wang, Q. Zhang, L. J. Zhang and Y. Q. Fan, *Synlett*, 2008, **2**, 233–236; (c) J. R. Li, X. Chen, D. X. Shi, S. L. Ma, Q. Li, Q. Zhang and J. H. Tang, *Org. Lett.*, 2009, **11**, 1193–1196; (d) L. P. Yang, D. X. Shi, S. Chen, H. X. Chai, D. F. Huang, Q. Zhang and J. R. Li, *Green Chem.*, 2012, **14**, 945–951; (e) M. X. Liu,



- J. R. Li, S. Chen, D. F. Huang, H. X. Chai, Q. Zhang and D. X. Shi, *RSC Adv.*, 2014, **4**, 35629–35634; (f) H. X. Chai, J. R. Li, L. P. Yang, H. Y. Lu, Q. Zhang and D. X. Shi, *RSC Adv.*, 2014, **4**, 44811–44814; (g) M. X. Liu, J. R. Li, H. X. Chai, K. Zheng, D. L. Yang, Q. Zhang and D. X. Shi, *Beilstein J. Org. Chem.*, 2015, **11**, 2125–2131; (h) J. J. Yang, D. X. Shi, P. F. Hao, D. L. Yang, Q. Zhang and J. R. Li, *Tetrahedron Lett.*, 2016, **57**, 2455–2461.
- 12 Y. M. Elkholy and M. A. Morsy, *Molecules*, 2006, **11**, 890–903.
- 13 (a) A. Pinner and F. Klein, *Ber. Dtsch. Chem. Ges.*, 1877, **10**, 1899; (b) A. P. Siskos and A. M. Hill, *Tetrahedron Lett.*, 2003, **44**, 789–792.
- 14 V. Y. Rozhkov, L. V. Batog, E. K. Shevtsov and M. I. Struchkova, *Mendeleev Commun.*, 2004, **2**, 76.
- 15 J. R. Li, H. X. Chai and L. P. Yang, *Chinese Pat.*, CN106967003A, 2017.

