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$ZnCl_2$-promoted domino reaction of 2-hydroxybenzonitriles with ketones for synthesis of 1,3-benzoxazin-4-ones†

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A $ZnCl_2$-promoted synthesis of 1,3-benzoxazin-4-one from 2-hydroxybenzonitriles 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.

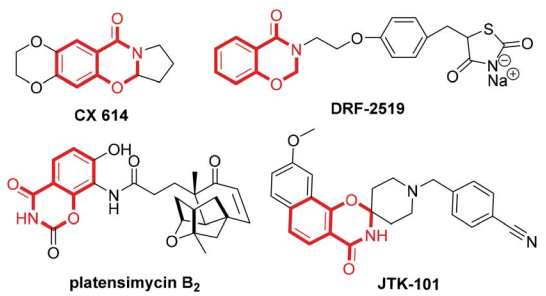
Introduction

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-6146,[2] DRF-2519,[3] platensimycin B_2 (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 colleagues[8] 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 (sp^3) 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-hydroxybenzonitrile 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-hydroxybenzonitrile **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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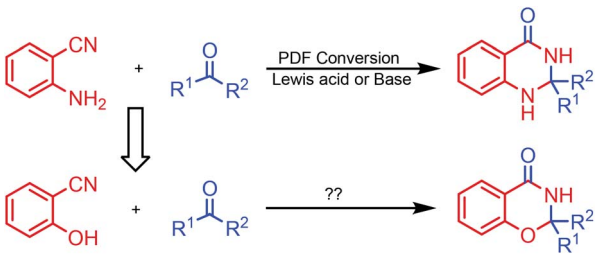
† Electronic supplementary information (ESI) available: The general experimental procedure and the characterization data of **3a–3o**. The crystal data of **3a**. The ^{1}H-NMR and ^{13}C-NMR spectra of products and HR-MS of new products. CCDC 1536185. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra04194k

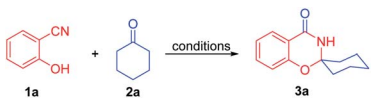


Scheme 2 Design synthesis of 4*H*-1,3-benzoxazin-4-ones.

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 cyclo-hexanone (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

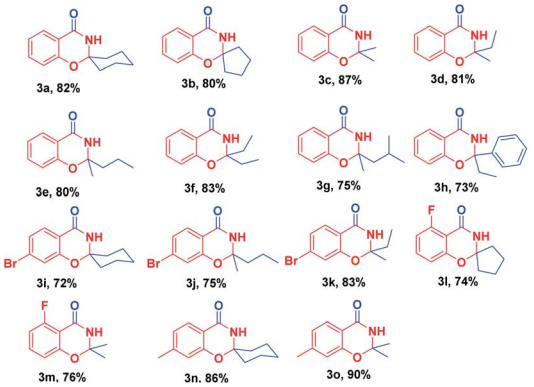
Table 1 Optimization of reaction conditions[a]



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.

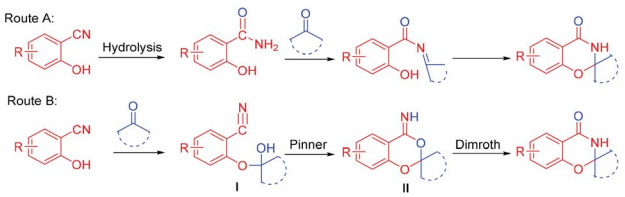
Table 2 Scope of substrates[a,b]



[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-4*H*-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*



Scheme 3 Possible reaction mechanisms.

an intramolecular Pinner reaction[13] results in the cyclized benzo[*d*][1,3]dioxin-4-imine **II**, which subsequently rearranges (Dimroth rearragement[14]) to afford the final product.

The chemical structures of target compounds **3** were characterized fully by spectroscopy (IR, ^{1}H NMR, ^{13}C 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 ^{1}H,^{1}H-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. ^{1}H and ^{13}C 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).

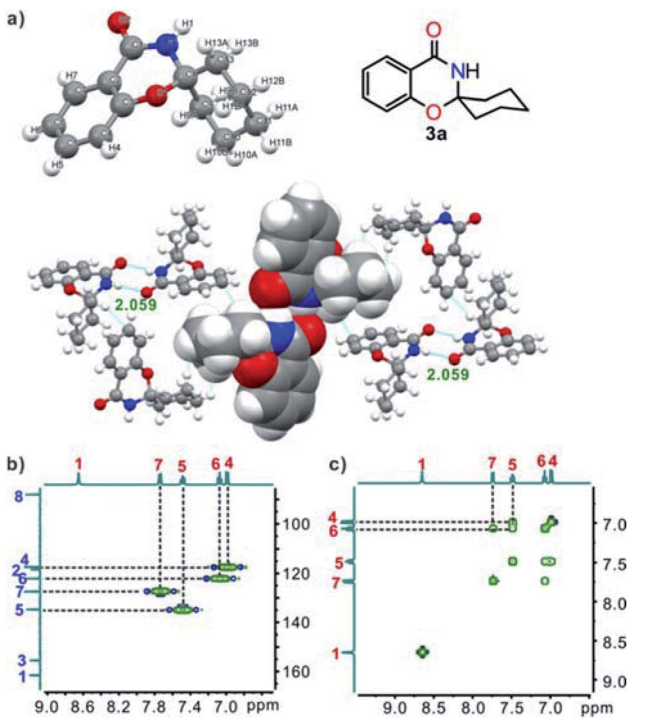


Fig. 1 (a) X-ray single-crystal structure and two-dimensional network of **3a** (O, red; N, blue; C, gray; H, white); (b) partial HSQC spectrum of **3a**; (c) partial ^{1}H–^{1}H COSY spectrum of **3a**.

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-hydroxybenzonitriles (1.0 mmol), $ZnCl_2$ (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 Na_2SO_4, 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, v, cm^{-1}): 3192, 3078, 2938, 2861, 1670, 1607, 1467, 770; ^{1}H-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); ^{13}C 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, v, cm^{-1}): 3192, 3078, 2938, 2861, 1670, 1607, 1467, 770; ^{1}H-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); ^{13}C 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, v, cm^{-1}): 3183, 3071, 2907, 1679, 1614, 1470, 754; ^{1}H-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); ^{13}C 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, v, cm^{-1}): 3180, 3062, 2970, 2933, 1671, 1614, 1470; ^{1}H-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

(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 ([M + H]$^+$).

2-Methyl-2-propyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1176.

2,2-Diethyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$).

2-Isobutyl-2-methyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{13}H_{18}NO_2$ 220.13321, found 220.13287.

2-Ethyl-2-phenyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{16}H_{16}NO_2$ 254.11756, found 254.11832.

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

White solid, m.p. 187–189 °C; IR (KBr, v, cm^{-1}): 3182, 3070, 2939, 2859, 1673, 1603, 1434; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{13}H_{15}BrNO_2$ 296.02776, found 296.02807.

7-Bromo-2-methyl-2-propyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{12}H_{15}BrNO_2$ 284.02776, found 284.02807.

7-Bromo-2,2-diethyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{12}H_{15}BrNO_2$ 284.02777, found 284.02807.

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

Yellow oil; IR (KBr, v, cm^{-1}): 3192, 3087, 2975, 2919, 1683, 1623; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{12}H_{13}FNO_2$ 222.09248, found 222.09243.

5-Fluoro-2,2-dimethyl-2,3-dihydro-4*H*-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; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{10}H_{11}FNO_2$ 196.07683, found 196.07671.

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

White solid, m.p. 200–202 °C; IR (KBr, v, cm^{-1}): 3186, 3075, 2936, 2919, 1678, 1621; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{14}H_{18}NO_2$ 232.13321, found 232.13344.

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

White solid, m.p. 164–166 °C; IR (KBr, v, cm^{-1}): 3181, 3071, 2990, 2912, 1677, 1618; ^{1}H-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 ([M + H]$^+$) m/z calcd for $C_{11}H_{14}NO_2$ 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-hydroxybenzonitriles 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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