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Facile synthesis of novel [1,3]oxazino[2,3-c][1,2,4] thiadiazin-12-one derivatives

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Abstract Several novel fused heterocyclic systems which have rings containing N/O or N/S have been synthesized through a facile one-pot method by the treatment of substituted 2-(benzo[d]thiazol-2-yl)phenol and cyanogen bromide in THF and NEt_3. This one-pot method contains tough ring-opening of thiazole, special intermolecular rearrangement and ring-closing reactions. The newly synthesized compounds were characterized by HR-MS, ^{1}H-NMR, ^{13}C-NMR spectral data and DFT calculation analysis. **2a** was also determined by X-ray crystallographic analysis.

Keywords Fused heterocyclic system · One-pot · Ring-opening · Ring-closing

Introduction

Heterocyclic derivatives containing more than one heteroatom (nitrogen, oxygen and sulfur) have become a topic of considerable interest in the recent literature. Nitrogen- and oxygen-containing heterocyclic derivatives, such as oxazines containing heterocyclic structures, may have optical activity [1], anticancer [2]

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and antidepressant activity [3], potassium channel opening activity [4], and potential neuroprotective properties [5]. Nitrogen- and sulfur-containing heterocyclic derivatives, such as thiadiazole, are potential drugs for antitumor [6, 7], antitubercular [8], antibacterial [9], antimicrobial [10], anticonvulsant [11] and herbicidal [12] activities. Over the past few years, the heterocyclic compounds have received much attention, as, with their diverse biological and pharmacology activities, they play an important role in medicine, pesticides, and materials and other intermediates in chemistry [13, 14].

Benzothiazole (Fig. 1) is a relatively stable universal heterocyclic compound, and its derivatives can be easily afforded through the structural modification at the 2-position [15–17]. Previous research has indicated that the ring-opening reaction can occur under harsh conditions using organometallic reagents [18]. Recently, some publications have reported the ring-opening reaction under mild conditions by adopting various copper or iron catalysts [19–23]. In addition, the work has been based on the benzothiazole derivative of substituted 2-(benzo[d]thiazol-2-yl)phenol (**1**). Usually, the reactive sites of 2-phenylbenzo[d]thiazole are the neighboring positions on substituted benzene (Fig. 1) [24–27]. For example, 2-(benzo[d]thiazol-2-yl)phenol (**1b**) (Fig. 1) was prepared by the reaction on this position [28]. In particular, there are rare reports about the thiazole ring extended reaction [20, 29]. The reactive sites of **1b** are normally on the phenol group [30–33] and some reactions also occur on the other positions [34–36]; meanwhile, the ring-change reaction on **1b** has not been published.

In this work, we report a facile, one-pot, no catalyst, room-temperature, short time method, based on the raw material of substituted 2-(benzo[d]thiazol-2-yl)phenol (**1a**–**j**). According to the special ring-opening, intermolecular rearrangement and ring-closing reaction, several novel fused heterocyclic systems which have N/O- and N/S-containing rings, [1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one derivatives (**2a**–**j**), have been synthesized (Scheme 1).

Experimental

Materials and instrumentation

All reagents and solvents were obtained from commercial sources and used without further purification, unless otherwise noted. All chromatographic separations were carried out on silica gel (300–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer at 298 K. $CDCl_3$ and DMSO-d_6 were

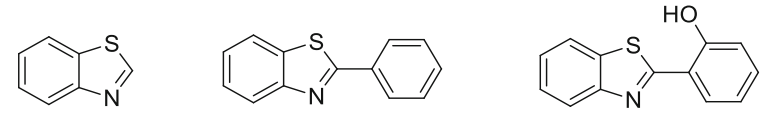
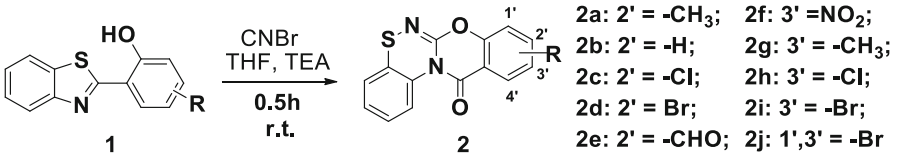


Fig. 1 The structures of benzothiazole, 2-phenylbenzo[d]thiazole and **1b**



Scheme 1 Synthesis of [1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one derivatives **2a–j**

used as solvent and TMS as internal reference. The chemical shifts were reported in parts per million (δ) relative to the appropriate reference signal: residual chloroform (δ_H 7.26) or DMSO (the quintet centered at 2.50 ppm). High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ FT Ultra instrument. X-Ray single crystal measurements for **2a** were carried out on a Xcalibur Eos diffractometer.

General procedure for the preparation of 2a–j

A solution of BrCN (157.5 mg, 1.5 mmol) in 1 mL anhydrous THF was cooled to 0 °C (dry ice bath) under nitrogen atmosphere in a 10-mL bottle. Then, a solution of **1a–j** (0.5 mmol) in 2 ml anhydrous THF and 10 dropwise NEt_3 was added dropwise, and the resulting solution was stirred at room temperature for 0.5 h under the nitrogen atmosphere. Then, the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel to afford products **2a–j.**

9-methyl-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one (**2a**): Yellow solid; $R_f = 0.29$ (DCM: PE = 3: 4), (20.7 mg, 0.074 mmol) yield: 14.7%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, $J = 8.0$ Hz, 1H), 7.59–7.50 (m, 1H), 7.25–7.17 (m, 2H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.06–7.01 (m, 1H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.54, 154.15, 148.01, 146.74, 130.86, 129.33, 128.56, 127.68, 127.44, 125.72, 123.89, 123.78, 115.94, 112.66, 22.00; HR-MS: calcd for $C_{15}H_{11}N_2O_2S$ [M + H^+], 283.0536; found 283.0537;

12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one**(2b):** Yellow solid, $R_f = 0.39$ (DCM: PE = 5: 6), (38.5 mg, 0.144 mmol) yield: 28.7%;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.70–7.62 (m, 1H), 7.61–7.54 (m, 1H), 7.34–7.27 (m, 2H), 7.26–7.22 (m, 1H), 7.20 (dd, $J = 8.3$, 1.0 Hz, 1H), 7.09–7.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.47, 154.16, 146.32, 136.11, 130.68, 129.34, 128.80, 127.78, 127.48, 124.53, 123.89, 123.79, 115.86, 115.23; HR-MS: calcd for $C_{14}H_9N_2O_2S$ [M + H^+], 269.0379; found 269.0381;

9-chloro-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2c):** Yellow solid, $R_f = 0.35$ (DCM: PE = 2: 3), (39.1 mg, 0.130 mmol) yield: 25.9%; ^{1}H NMR (400 MHz, DMSO) δ 7.97 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 1.9$ Hz, 1H), 7.53–7.47 (m, 1H), 7.42 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.34–7.27 (m, 2H), 7.25–7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.71, 154.38, 145.45, 142.16, 130.45, 129.89, 129.14, 127.93, 127.59, 125.25, 123.90, 123.80, 116.23, 113.83; HRMS: calcd for $C_{14}H_8N_2O_2SCl$ [M + H^+], 302.9990; found 302.9989;

9-bromo-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2d):** Yellow solid, $R_f = 0.31$ (DCM: PE = 1:1), (45.8 mg, 0.133 mmol) yield:

26.5%; ^{1}H NMR (400 MHz, DMSO) δ 7.87 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.55 (dd, J = 8.4, 1.8 Hz, 1H), 7.51–7.45 (m, 1H), 7.32–7.26 (m, 2H), 7.24–7.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.86, 154.27, 145.40, 130.46, 129.92, 129.18, 128.16, 127.97, 127.61, 123.93, 123.82, 119.22, 114.26; HR-MS: calcd for $C_{14}H_8BrN_2O_2S$ [M + H^+], 346.9484; found 346.9485;

12-oxo-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazine-9-carbaldehyde **(2e):** Yellow solid, R_f = 0.38 (DCM: PE = 3: 2), (15.5 mg, 0.053 mmol) yield: 10.5%; ^{1}H NMR (400 MHz, DMSO) δ 10.09 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.89–7.72 (m, 2H), 7.60–7.45 (m, 1H), 7.38–7.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.20, 153.83, 141.35, 128.98, 128.57, 127.94, 127.39, 124.22, 124.05, 123.92, 120.15, 116.59; HR-MS: calcd for $C_{15}H_9N_2O_3S$ [M + H^+], 297.0328; found 297.0328;

10-nitro-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2f):** Yellow solid, R_f = 0.38 (DCM: PE = 2: 1), (43.5 mg, 0.139 mmol) yield: 27.8%; ^{1}H NMR (400 MHz, DMSO) δ 8.61 (d, J = 2.8 Hz, 1H), 8.54 (dd, J = 9.1, 2.8 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.54–7.49 (m, 1H), 7.35–7.29 (m, 2H), 7.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 157.19, 156.22, 145.47, 143.46, 130.63, 130.01, 128.24, 128.04, 127.46, 124.12, 123.90, 123.20, 117.45, 116.90; HR-MS: calcd for $C_{14}H_8N_3O_4S$ [M + H^+], 314.0230; found 314.0230;

10-methyl-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2 g):** Yellow solid, R_f = 0.29 (DCM: PE = 2: 3), (15.2 mg, 0.054 mmol) yield: 10.8%; ^{1}H NMR (400 MHz, DMSO) δ 7.78 (s, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.61–7.53 (m, 1H), 7.52–7.45 (m, 1H), 7.35–7.26 (m, 2H), 7.26–7.17 (m, 2H), 2.40–2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 157.40, 151.64, 147.12, 137.02, 134.03, 130.48, 128.68, 127.75, 127.66, 127.36, 124.17, 123.93, 115.53, 115.08, 20.07; HR-MS: calcd for $C_{15}H_{11}N_2O_2S$ [M + H^+], 283.0536; found 283.0534;

10-chloro-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2 h):** Yellow solid, R_f = 0.33 (DCM: PE = 1: 1), (108.7 mg, 0.360 mmol) yield: 72.0%; ^{1}H NMR (400 MHz, DMSO) δ 7.91 (d, J = 2.6 Hz, 1H), 7.80 (dd, J = 8.8, 2.7 Hz, 1H), 7.53–7.47 (m, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.33–7.27 (m, 2H), 7.26–7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.44, 152.64, 145.43, 136.04, 130.41, 130.15, 129.26, 128.22, 128.01, 127.64, 123.93, 123.80, 117.50, 116.44; HR-MS: calcd for $C_{14}H_8ClN_2O_2S$ [M + H^+], 302.9990; found 302.9990;

10-bromo-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2i):** Yellow solid, R_f = 0.22 (DCM: PE = 2: 3), (92.2 mg, 0.267 mmol) yield: 53.3%; ^{1}H NMR (400 MHz, DMSO) δ 8.03 (d, J = 2.4 Hz, 1H), 7.91 (dd, J = 8.8, 2.5 Hz, 1H), 7.52–7.46 (m, 1H), 7.37–7.27 (m, 3H), 7.25–7.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.31, 153.13, 145.38, 138.88, 131.26, 130.38, 129.25, 128.02, 127.65, 123.94, 123.80, 117.77, 117.22, 116.81; HR-MS: calcd for $C_{14}H_8BrN_2O_2S$ [M + H^+], 346.9483; found 346.9483;

8,10-dibromo-12H-benzo[e]benzo[5,6][1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one **(2j):** Yellow solid, R_f = 0.37 (DCM: PE = 1: 1), (63.6 mg, 0.150 mmol) yield: 30.0%; ^{1}H NMR (400 MHz, DMSO) δ 8.30 (d, J = 2.3 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), 7.47 (dd, J = 6.0, 3.4 Hz, 1H), 7.31 (dd, J = 6.0, 3.4 Hz, 2H),

7.23 (dd, $J = 5.8$, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.60, 150.47, 144.08, 141.37, 130.47, 130.07, 129.13, 128.21, 127.74, 123.91, 123.78, 117.68, 117.19, 110.33; HR-MS: calcd for $C_{14}H_7Br_2N_2O_2S$ [M + H^+], 424.8589; found 424.8588;

Result and discussion

By the treatment of substituted 2-(benzo[d]thiazol-2-yl)phenol and cyanogen bromide in THF and NEt_3, the resulting solution was stirred for 0.5 h at room temperature, and the solution changed from white to yellow. After silica gel column chromatography, ten new heterocyclic compounds were afforded (**2a**–**j**) with yields of 10.5–72%. All these compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and HR-MS, and **2a** was further characterized by X-ray crystallographic analysis.

According to the ^{1}H-NMR spectrum of **1a** (Fig. 2a), a typical proton signal (–OH) appeared at 12.46 ppm, methyl proton signals (–CH_3) at 2.37 ppm, seven phenyl proton signals in the region of 6.70–8.05 ppm which include four doublets (d, 7.96, 7.89, 7.56, 6.77 ppm, respectively), two triplet of doublets (td) and one singlet (s). In the ^{1}H-NMR spectrum of the new heterocyclic conpound **2a** (Fig. 2b),the low shift signal around 12 ppm disappeared which represents the disappearance of the hydroxy group. No such change on other parts of ^{1}H-NMR spectrum was observed except the shift of signals on phenyl, in agreement with the presence of two phenyl rings.

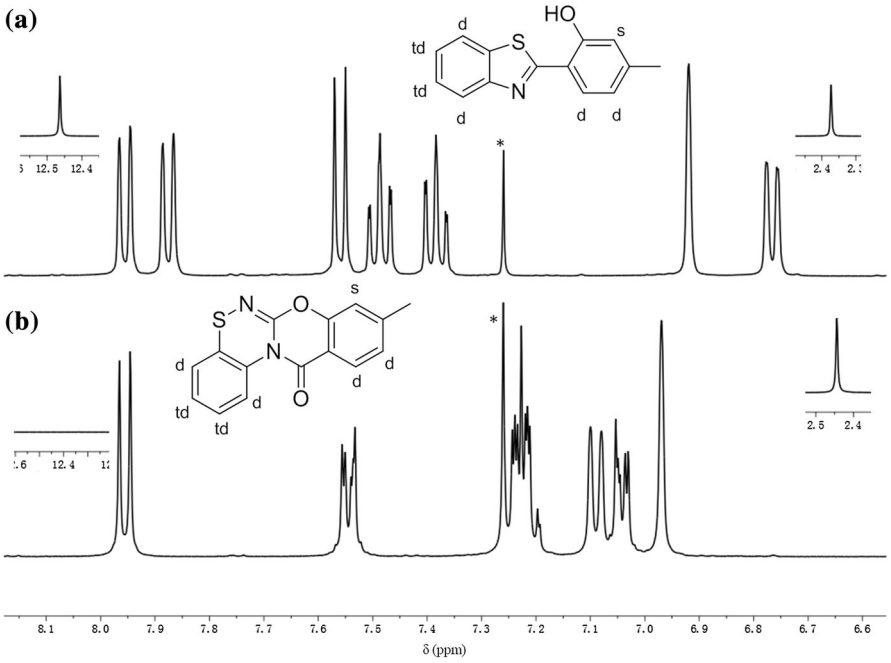


Fig. 2 ^{1}H-NMR spectra of **a 1a** and **b 2a** in $CDCl_3$ at 298 K. *Asterisk* the residual solvent signal

To further elucidate the structure of the products, a high-resolution mass spectrum (HR-MS) of each compounds was obtained. The experimental results are also consistent with the formulation above. In **2a**, for example, the calculated HR-MS of **2a** ($C_{15}H_{10}N_2O_2S$ [M + H^+]) is 283.0536, which is agreement with the experimental HR-MS, 283.0537.

The unambiguous explicit structural determination of **2a** was afforded by X-ray diffraction analysis (Fig. 3a). In the crystal, the structure of **2a** revealed a nonplanar skeleton because of the non-conjugated thiadiazole heterocyclic. The distortion of this compound can be measured by crystal analysis, and the distance of the sulfur atom to the planar of **2a** (m.d.: oxazines and the conjugated benzene ring defined as macrocycle planar) is estimated to be 1.002 Å (Fig. S1). The angles and bond lengths of the novel fused ring ([1,3]oxazino[2,3-c][1,2,4]thiadiazin-12-one) are summarized in Tables S1 and S2.

To further understand the reaction process of this ring-changing reaction, on the basis of the product X-ray structure, a plausible mechanism is proposed in Scheme 2. First, the nucleophilic substitution of the phenol group on **1** to the cyanogen bromide affords intermediate **A**. After the hydrolysis of cyanogroup on **A**, **B** was obtained. Then, the intramolecular nucleophilic addition of the sulfur atom in the benzothiozole can afford **C**. Next, ring-opening of benzothiozole followed by nucleophilic addition to N–C triple bond in the presence of water and isomerization reaction occurs to produce **E**. Finally, the ring-closing reaction of **E** and the subsequent dehydration reaction provided the corresponding product **2**.

In conclusion, a new family of heterocyclic compounds which have N/O- and N/S-containing ring fused heterocycles can be obtained by a facile one-pot reaction with no catalyst. The reaction can occur rapidly in mild conditions. This process contains a normal tough ring-opening, a special intermolecular rearrangement and a ring-closing reaction. All the new compounds were characterized by HR-MS, ^{1}H-NMR, ^{13}C-NMR spectral data and DFT calculation analysis. **2a** was determined by X-ray crystallographic analysis. This new kind of heterocyclic compound may also

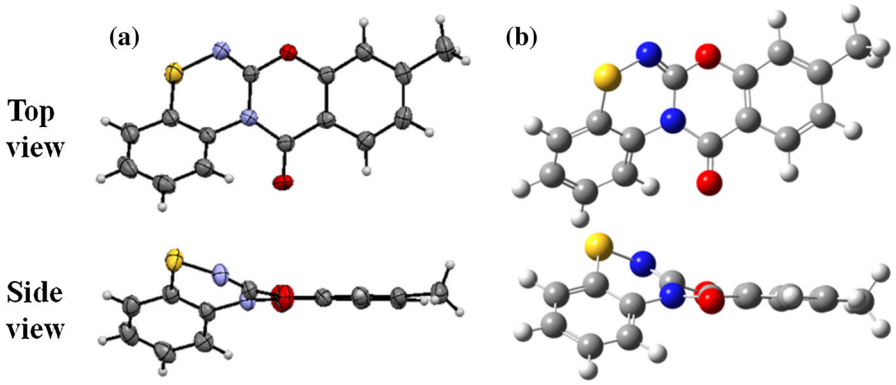
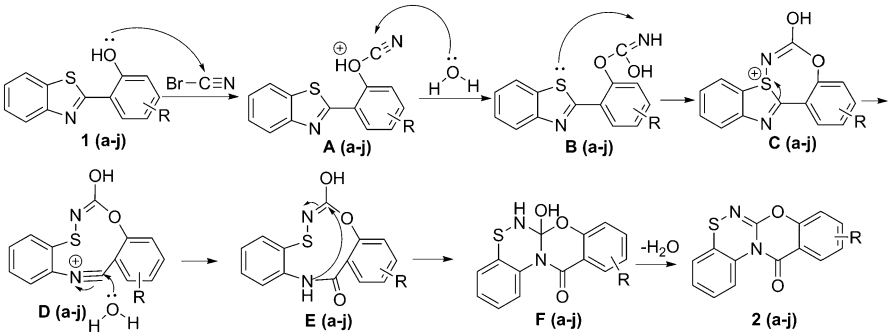


Fig. 3 Top view and side view of X-ray crystal structures (**a**) and optimized structures (**b**) of **2a**. The thermal *ellipsoids* represent 50% probability; Optimized structures obtained by DFT (B3LYP/6-31G*) calculations. The detailed crystallographic data are in Table S3



Scheme 2 A plausible mechanism of the synthesis of [1,3]oxazino[2,3-c][1,2,4] thiadiazin-12-one derivatives **2a–j**

have potential applications in biology and pharmacology, and further applications of **2a–j** for the investigation of biological activity in biosystems are under progress.

Supplementary material

Supplementary data (the detailed synthetic procedures, characterization, NMR spectra and DFT calculation datas, CCDC of **2a** is 1511615) associated with this article can be found in the online version.

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