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Exploring the Reactivity of 2-Trichloromethylbenzoxazoles for Access to Substituted Benzoxazoles

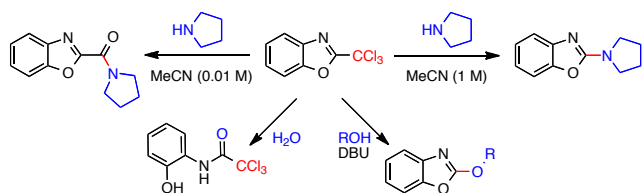
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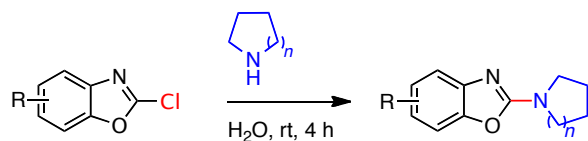


The reactivity of 2-trichloromethylbenzoxazoles towards various nucleophiles, under metal free or iron-catalyzed conditions, for the synthesis of substituted benzoxazoles is described. These methods allow for selective substitution at either the 2- or 2'- position of the benzoxazoles using the same starting materials / reagents. This approach allows for the controlled synthesis of a variety of key derivatives from a single 2-trichloromethylbenzoxazole starting material.

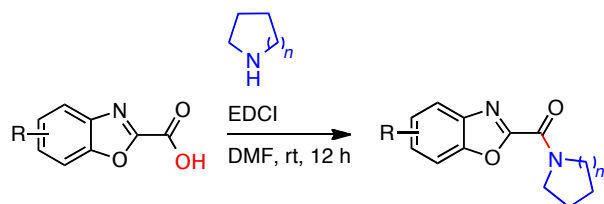
The benzoxazole motif has been incorporated into a number of pharmaceuticals, agrochemicals and materials that are vital to our everyday lives.¹ Due to the importance of benzoxazoles, widespread research has been conducted on their synthesis² and subsequent functionalization.³ The selective synthesis of 2-amino- or 2-amidobenzoxazoles from both activated substrates^{4,5} and via C-H^{6,7} activation has been extensively developed (Scheme 1a/b).^{4a,5b} Due to the nature of the methods used for their synthesis either the 2-amino- or 2-amidobenzoxazoles can be accessed, but generally not both from the same starting materials using the same reagents. Additionally, in order to mitigate the negative environmental and cost implications of noble metal catalysts, there has been a recent push to develop metal free or base metal-catalyzed methods.^{8,9} Thus an opportunity exists to develop selective synthetic methods for the derivatization of this important scaffold. Previously, we showed that 2-trichloromethylbenzoxazoles **1** could be synthesized via a mild, metal free reaction between trichloroacetonitrile¹⁰ and 2-aminophenols **4** in methanol at 40 °C (*cf.* Scheme 2).^{11,12} Whilst the reactivity of some 2-trichloromethylazoles has been investigated,¹³ little work on the reactivity of 2-

trichloromethylbenzoxazoles has been reported.¹⁴ Herein we report our findings into controlling the reactivity of 2-trichloromethylbenzoxazoles for the selective synthesis of 2-amino- or 2-amidobenzoxazoles as well as other derivatives in which the carbon of the trichloromethyl moiety is either extruded or retained (Scheme 1c).

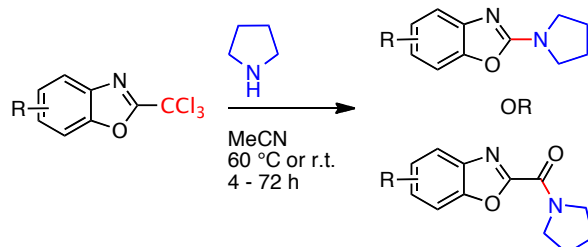
Metal free synthesis of 2-aminobenzoxazoles (a)^{4a}



Metal free synthesis of 2-amidobenzoxazoles (b)^{5b}

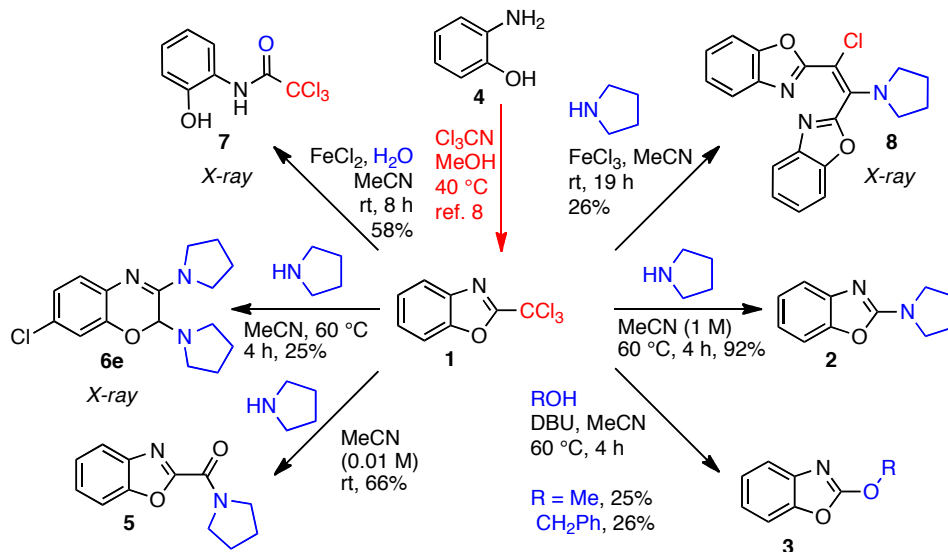


This Work - Selective synthesis of 2-amino- or 2-amido-benzoxazoles from 2-trichloromethylbenzoxazoles (c)



Scheme 1. Methods of benzoxazole functionalization

Due to the importance of 2-aminobenzoxazoles, the study began with the direct displacement of the 2-trichloromethyl moiety from 2-(trichloromethyl)benzo[*d*]oxazole **1** with an amine nucleophile.¹⁵ Initial reactions resulted in a mixture of 2-amino- and 2-amidobenzoxazoles. After screening a variety of Lewis acids, which were hoped to activate the C-2 position towards nucleophilic aromatic substitution, as well as solvents, temperatures and times it was found that the key parameters for controlling the product distribution between amine **2** and amide **5** were the molarity of the system and water content.¹⁶ Thus, reaction of 2-trichloromethylbenzoxazole **1** with pyrrolidine (1.1 equiv.) in dry acetonitrile (1 M, relative to the benzoxazole) at 60 °C for 4 h afforded the desired 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2**) in excellent yield. The reaction could also be run at rt, though required 13 h to go to completion, or in the presence of the nucleophilic catalysts DABCO,¹⁷ which led to slightly improved yields (*cf.* Scheme 3). Interestingly, based on pK_aH values the reaction should



Scheme 2. DOS approach to the functionalization of 2-(trichloromethyl)benzo[*d*]oxazole (**1**)

not proceed (*cf.* Scheme S1).¹⁸ It is believed that the liberated chloroform decomposes under the reaction conditions to form a reactive carbene intermediate, which then decomposes and thus shifts the reaction equilibrium towards the 2-amino product **2**.¹⁹

Building upon the selective C-2 substitution of an amine nucleophile, the addition of an alkoxide,²⁰ generated *in situ*, to the 2-position of the trichloromethylbenzoxazole was investigated. It was found that methanol and benzyl alcohol could add effectively to 2-(trichloromethyl)benzo[*d*]oxazole (**1**) in the presence of DBU in acetonitrile to form either 2-methoxybenzo[*d*]oxazole (**3a**) or 2-(benzyloxy)benzo[*d*]oxazole (**3b**), albeit in moderate yields. It was previously reported that strong bases can be used in the addition of alcohols to related trichloromethylazoles.¹³ Unfortunately, these conditions did not lead to an improved yield of the desired addition adducts.

Having established methods for the direct C-2 substitution of 2-trichloromethylbenzoxazoles, the selective C-2' substitution processes were investigated.²¹ After screening a variety of conditions¹⁶ it was found that reaction of 2-(trichloromethyl)benzo[*d*]oxazole (**1**) with pyrrolidine (0.9 equiv.) in wet acetonitrile (0.01 M, relative to the benzoxazole) at rt for 76 h afforded the desired benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**) in 66% yield. Reducing the reaction time to 19 h gave the product in 35% yield. These mild conditions are in contrast to related amide forming processes from heterocyclic trichloromethyl groups that use strong bases, high reaction temperatures or toxic solvents to achieve similar transformations.²⁰ They therefore should be particularly applicable to substrates that are base or thermally unstable. It was also possible to reduce the reaction time via the addition of FeCl₃ (1.0 equiv.), which

resulted in the formation of benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**) after 19 h in 57% yield.

As part of a substrate scope study (*vide infra*) it was found that the reaction of 2-(trichloromethyl)benzo[*d*]oxazole (**1**) with pyrrolidine (1.1 equiv.) in acetonitrile (1 M relative to the pyrrolidine) at 60 °C for 4 h afforded 7-chloro-2,3-di(pyrrolidin-1-yl)-2*H*-benzo[*b*][1,4]oxazine (**6e**), the structure of which was confirmed by X-ray analysis.²² Gauß and Heitzer previously reported a related ring expansion process, though they started from 2-dichloromethylbenzoxazoles rather than 2-trichloromethylbenzoxazole **1**.²³ Also, Molinski *et al.* found that 2-substituted oxazolines could be converted to dihydrooxazinones in the presence of SeO₂.²⁴ Interestingly, compound **6e** could only be formed if a reduction was taking place under the reaction conditions, though at which point in the process the reduction is taking place is unclear. In related work, it was also shown that 2-dichloromethylbenzoxazoles can undergo hydrogen / deuterium exchange in the presence of triethylamine.

Furthermore, hydrolysis of 2-trichloromethylbenzoxazole **1** was examined (Scheme 2). It was found that upon treatment of 2-(trichloromethyl)benzo[*d*]oxazole (**1**) with FeCl₂ (2 mol %) and H₂O (2.5 equiv.)²⁵ that ring opened 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (**7**) was formed in good yield. The connectivity of acetamide **7** was confirmed by X-ray analysis.²² Acetamide **7** and related analogues have previously been shown to have germination inhibition activity against lettuce seeds.²⁶ A screen of hydrolysis condition was undertaken to investigate this process further. It was found that the best non-metal containing process for the hydrolysis was to heat 2-trichloromethylbenzoxazole **1** in H₂O at 150 °C for 2 h. This method gave the desired 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (**7**) in a moderate 37% yield.²²

In efforts to optimize the addition reactions and control the C-2 vs. C-2' selectivity a variety of Lewis acids were screened.²² During the course of this study it was found that the reaction of 2-trichloromethylbenzoxazole (**1**) with pyrrolidine (1.1 equiv.) in the presence of FeCl₃ afforded bisbenzoxazole **8** in moderate yield. The structure of this novel compound was confirmed by 2D NMR analysis and X-ray crystallography.²²

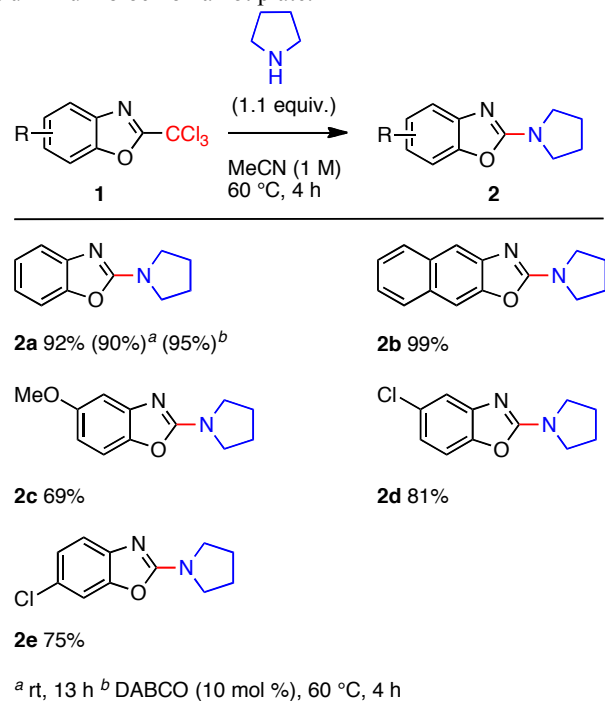
With the optimized conditions in hand for the synthesis of 2-aminobenzoxazoles, the effect of substitution on the benzoxazole ring was investigated to assess the effect of electronic factors on the formation of 2-aminobenzoxazoles **2** from 2-trichloromethylbenzoxazoles **1** (Scheme 3). Thus, reaction of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**) with pyrrolidine (1.1 equiv.) at either 60 °C / rt afford 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2a**) in excellent yield. The addition of the nucleophilic catalyst DABCO (10 mol %) lead to a slight increase in yield of 2-aminobenzoxazole **2a**.¹⁷ The annulation of an aromatic ring to the starting material lead to an increased yield of 2-(pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (**2b**). Interestingly, having an electron rich methoxy moiety in the system resulted in a decrease in yield of **2c** relative to the electron deficient 5- and 6-chloro derivatives, **2d** and **2e**. As mentioned previously, the mass balance in the reaction of the chloro-substituted benzoxazoles **1d** / **1e** are the ring opened species **6d** / **6e** (cf. Scheme 2).

In conclusion, an investigation into the reactivity of 2-trichloromethylbenzoxazole towards various nucleophiles under metal free or iron-catalyzed conditions was conducted. The newly developed methods allow for the controlled synthesis of a variety of benzoxazole derivatives starting from the same starting material. Importantly, these methods allow for substitution at either the 2- or 2'- position of the benzoxazoles by simply altering the reactant concentration / water content. Thus a variety of derivatives can be synthesized from a simple 2-trichloromethylbenzoxazole starting material via this diversity-oriented synthesis (DOS)²⁷ type approach.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. Solvents used for column chromatography were of technical grade. Column chromatography was performed on silica gel (60-120) mesh. Visualization was accomplished with UV light and a potassium permanganate solution. ¹H NMR and ¹³C NMR were recorded at ambient temperature using CDCl₃ (7.26 ppm). Chemical shift values are expressed as parts per million (ppm) and *J* values are in Hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet or combination, br.s broad singlet or m: multiplet. The melting points reported are uncorrected. Infrared spectra were recorded as diluted solutions, in spectroscopic grade chloroform unless otherwise stated. Absorption maxima (λ_{max}) of major peaks are reported in wavenumbers (cm⁻¹), quoted to the nearest integral wavenumber. Reactions were

run in a sealed microwave reaction vessel and heated using an aluminium block on a hot plate.



Scheme 3. Addition of pyrrolidine to substituted 2-trichloromethylbenzoxazoles

2-(Pyrrolidin-1-yl)benzo[*d*]oxazole (2a**)**²⁸ *Method A:* To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 200 mg, 0.8 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (79 μL, 0.9 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2a**, 146 mg, 92% yield) as a yellow solid. *Method B:* To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 200 mg, 0.8 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (79 μL, 0.9 mmol). The resultant solution was stirred at r.t. for 13 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2a**, 143 mg, 90% yield) as a yellow solid. *Method C:* To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 100 mg, 0.42 mmol) in dry acetonitrile (1 M) at r.t. were added pyrrolidine (40 μL, 0.47 mmol) and DABCO (4.7 mg, 0.042 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2a**, 75 mg, 95% yield) as a yellow solid. m.p. 133 – 135 °C (lit. m.p. 136 – 137 °C); *R*_f = 0.25 (1:9 ethyl acetate:petroleum ether); IR (CHCl₃) $\nu(\text{cm}^{-1})$ 3011, 2978, 2880, 1648; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_{H} 7.36 (1H, d, *J* = 7.8 Hz), 7.26 (1H, d, *J* = 7.8 Hz), 7.15 (1H, apparent td, *J* = 7.7, 1.2 Hz), 6.99 (1H, apparent td, *J* = 7.7, 1.2 Hz), 3.69 – 3.62 (4H, m), 2.07 – 2.01

(4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 160.9, 148.9, 143.5, 123.6, 119.9, 115.8, 108.4, 47.2 (2C), 25.4 (2C); HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}^+$, 189.1023, found: 189.1030.

2-(Pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (2b) To a stirred solution of 2-(trichloromethyl)naphtho[2,3-*d*]oxazole (**1b**, 158 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (**2b**, 130 mg, 99% yield) as a yellow oil. IR (CHCl_3) $n(\text{cm}^{-1})$ 2969, 2881, 1656; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.86 – 7.80 (2H, m), 7.68 (1H, s), 7.58 (1H, s), 7.37 (2H, quind, $J = 6.9$, 1.3 Hz), 3.66 (4H, t, $J = 6.7$ Hz), 2.05 – 1.97 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.9, 149.3, 144.1, 131.9, 129.2, 127.6, 127.5, 124.2, 123.5, 111.4, 104.3, 47.5 (2C), 25.5 (2C); HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}^+$, 239.1179, found: 239.1189.

5-Methoxy-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (2c)²⁹ To a stirred solution of 5-methoxy-2-(trichloromethyl)benzo[*d*]oxazole (**1c**, 147 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 5-methoxy-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2c**, 83 mg, 69% yield) as a light brown crystals. IR (CHCl_3) $n(\text{cm}^{-1})$ 2957, 2880, 1650; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.10 (1H, d, $J = 8.6$ Hz), 6.92 (1H, d, $J = 2.5$ Hz), 6.53 (1H, dd, $J = 8.6$, 2.5 Hz), 3.79 (3H, s), 3.64 – 3.60 (4H, m), 2.04 – 1.99 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.8, 156.9, 144.7, 143.6, 108.3, 106.3, 101.2, 55.8, 47.3 (2C), 25.6 (2C); HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2^+$, 219.1129, found: 219.1134.

5-Chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (2d)²⁹ To a stirred solution of 5-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**1d**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 5-chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2d**, 100 mg, 81% yield) as a white solid. m.p. 121 – 123 °C; IR (CHCl_3) $n(\text{cm}^{-1})$ 2979, 2882, 1650; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.28 (1H, d, $J = 2.1$ Hz), 7.10 (1H, d, $J = 8.4$ Hz), 6.90 (1H, dd, $J = 8.4$, 2.1 Hz), 3.60 (4H, t, $J = 6.7$ Hz), 2.05 – 1.96 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.6, 147.5, 145.0, 128.9, 119.6, 115.8, 108.9, 47.3 (2C), 25.4 (2C); HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{11}\text{H}_{12}\text{ClN}_2\text{O}^+$, 223.0633, found: 223.0637.

6-Chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (2e) To a stirred solution of 6-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**1e**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μL , 0.6 mmol). The

resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 6-chloro-2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**2e**, 93 mg, 75% yield) as a white solid. m.p. 126 – 128 °C; IR (CHCl_3) $n(\text{cm}^{-1})$ 2979, 2881, 1651; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.22 – 7.19 (2H, m), 7.08 – 7.00 (1H, m), 3.62 – 3.58 (4H, m), 2.05 – 1.96 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.2, 149.1, 142.6, 125.0, 124.0, 116.1, 109.3, 47.4 (2C), 25.5 (2C); HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{11}\text{H}_{12}\text{ClN}_2\text{O}^+$, 223.0633, found: 223.0639.

2-Methoxybenzo[*d*]oxazole (3a)³⁰ To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 150 mg, 0.6 mmol, 1 equiv.) in acetonitrile (0.6 mL, 1 M) at ambient temperature were added methanol (28 μL , 0.7 mmol, 1.1 equiv.) and DBU (104 μL , 0.7 mmol, 1.1 equiv.). The resultant solution was stirred at 60 °C for 16 h. The mixture was allowed to cool to r.t. and filtered through silica (dichloromethane). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on base washed silica gel (3% ethyl acetate in petroleum ether) to afford 2-methoxybenzo[*d*]oxazole (**3a**, 24 mg, 25%) as a clear oil. $R_f = 0.50$ (1:2 ethyl acetate:petroleum); IR (CHCl_3) $n(\text{cm}^{-1})$ 3156, 2927, 2254, 1792, 1747, 1552; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.90 (1H, d, $J = 7.9$ Hz) 7.67 (1H, d, $J = 8.1$ Hz), 7.56 – 7.44 (2H, m), 4.10 (3H, s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 156.9, 150.9, 140.5, 128.3, 125.9, 122.2, 111.8, 53.7; HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_8\text{H}_8\text{NO}_2^+$, 150.0550, found: 150.0540.

2-(Benzoyloxy)benzo[*d*]oxazole (3b)³¹ To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 150 mg, 0.6 mmol, 1 equiv.) in acetonitrile (0.6 mL, 1 M) were added benzyl alcohol (73 μL , 0.7 mmol, 1.1 equiv.) and DBU (104 μL , 0.7 mmol, 1.1 equiv.). The resultant solution was stirred at 60 °C for 16 h. The mixture was allowed to cool to r.t. and filtered through silica (dichloromethane). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on base washed silica gel (1% ethyl acetate in petroleum ether) to afford 2-(benzyloxy)benzo[*d*]oxazole (**3b**, 37 mg, 26%) as a clear oil. IR (CHCl_3) $n(\text{cm}^{-1})$ 3009, 2928, 2855, 1741, 1613, 1568; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.81 – 7.79 (2H, m) 7.64 – 7.62 (2H, m), 7.47 (2H, apparent td, $J = 7.7$, 1.4 Hz), 7.42 – 7.35 (3H, m), 6.87 (2H s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 159.6, 151.0, 140.1, 128.6, 128.3, 126.9 (2C), 125.3 (2C), 121.2 (2C), 119.4, 111.3, 61.0; HRMS (ESI) m/z : calculated for $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{12}\text{NO}_2^+$, 226.0863, found: 226.0873.

Benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (5) Method A: To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 100 mg, 0.42 mmol) in acetonitrile (0.01 M) at ambient temperature was added pyrrolidine (40 μL , 0.47 mmol). The resultant solution was stirred at ambient temperature for 76 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 60 mg, 66%) as a yellow solid. **Method B:** To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 100 mg, 0.42 mmol) in

acetonitrile (0.01 M) at ambient temperature was added pyrrolidine (40 μ L, 0.47 mmol). The resultant solution was stirred at ambient temperature for 19 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 32 mg, 35%) as a yellow solid. *Method C*: To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 100 mg, 0.42 mmol) in acetonitrile (0.01 M) at ambient temperature were added iron(III)chloride (68 mg, 0.42 mmol) and pyrrolidine (40 μ L, 0.47 mmol). The resultant solution was stirred at ambient temperature for 19 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[*d*]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 52 mg, 57%) as a yellow solid. m.p. 126-128 °C; R_f = 0.20 (1:9 ethyl acetate:petroleum ether) IR (CHCl₃) ν (cm⁻¹) 3006, 2886, 1640; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.83 (1H, d, J = 7.5 Hz) 7.66 (1H, d, J = 7.6 Hz) 7.48 – 7.42 (2H, m), 4.14 (2H, t, J = 6.8 Hz), 3.76 (2H, t, J = 6.8 Hz), 2.11 – 1.93 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 155.8, 155.3, 150.1, 140.6, 127.2, 125.2, 121.4, 111.7, 49.3, 47.5, 26.5, 23.9; HRMS (ESI) m/z : calculated for [M+H]⁺, C₁₂H₁₃N₂O₂⁺, 217.0972, found: 217.0970.

6-Chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[*b*][1,4]oxazine (6d) To a stirred solution of 5-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**1d**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μ L, 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 6-chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[*b*][1,4]oxazine (**6d**, 24 mg, 14% yield) as a yellow gummy solid. IR (CHCl₃) ν (cm⁻¹) 3690, 2929, 2876, 1610; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.08 (1H, d, J = 2.1 Hz), 6.80 – 6.72 (2H, m), 5.45 (1H, s), 3.65 (3H, br.s), 3.36 (1H, br.s) 2.96 – 2.89 (2H, m) 2.68 – 2.61 (2H, m) 1.97 (4H, br.s) 1.72 – 1.60 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 152.3, 144.7, 136.0, 125.8, 123.3, 121.9, 115.0, 80.2, 46.7 (4C), 24.4 (4C); HRMS (ESI) m/z : calculated for [M+H]⁺, C₁₆H₂₁ClN₃O⁺, 306.1368, found: 306.1373.

7-Chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[*b*][1,4]oxazine (6e) To a stirred solution of 6-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**1e**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at r.t. was added pyrrolidine (51 μ L, 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 7-chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[*b*][1,4]oxazine (**6e**, 42 mg, 25% yield) as a yellow gummy solid. IR (CHCl₃) ν (cm⁻¹) 3667, 2974, 2876, 1607; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.01 (1H, dd, J = 7.9, 0.7 Hz), 6.84 – 6.80 (2H, m), 5.46 (1H, s), 3.63 (3H, br.s), 3.37 (1H, br.s) 2.96 – 2.88 (2H, m) 2.68 – 2.61 (2H, m) 2.01 – 1.94 (4H, m) 1.69 – 1.60 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 151.8, 146.5, 133.5, 126.6, 124.1, 121.3, 114.6, 80.2, 46.6 (4C), 24.4 (4C); HRMS (ESI) m/z : calculated for [M+H]⁺, C₁₆H₂₁ClN₃O⁺, 306.1368, found: 306.1360.

2,2,2-Trichloro-*N*-(2-hydroxyphenyl) acetamide (**7**)³²

Method A: To a stirred solution of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 237mg, 1 mmol, 1 equiv.) and iron(III) chloride (3.0 mg, 0.02 mmol, 2 mol %) in acetonitrile (0.2 mL, 5 M) at r.t. was added water (18 μ L, 1 mmol, 1.0 equiv.). The resultant mixture was stirred at r.t. for 5 h. Water (27 μ L, 1.5 mmol, 1.5 equiv.) was added. The mixture was stirred at r.t. for 3 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (**7**, 148 mg, 58%) as a yellow solid. *Method B*: 2-(Trichloromethyl)-benzo[*d*]oxazole (**1a**, 61 mg, 0.26 mmol) in H₂O (1.0 mL) was stirred at 150 °C for 2 h. The solution was allowed to cool to r.t. and dichloromethane (10 ml) was added. The resultant solution was washed with water (3 x 5 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to afford 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (**7**, 24 mg, 37%) as a yellow solid. m.p. 160 - 161 °C (lit. m.p. 160 °C); IR (CHCl₃) ν (cm⁻¹) 3594, 3397, 1720, 1615; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 8.98 (1H, br.s) 7.95 (1H, d, J = 8.0 Hz), 7.13 – 7.09 (1H, m), 7.02 – 6.93 (2H, m) 5.99 (1H br.s); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 159.7, 146.1, 126.6, 124.5, 121.7, 121.2, 116.5, 92.5; HRMS (ESI) m/z : calculated for [M+H]⁺, C₈H₇Cl₃NO₂⁺, 253.9537, found: 253.9534.

(*Z*)-2,2'-(1-Chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[*d*]oxazole) (8**)** To a stirred suspension of 2-(trichloromethyl)benzo[*d*]oxazole (**1a**, 150 mg, 0.6 mmol, 1.0 equiv.) and iron(III) chloride (97mg, 0.6 mmol, 1.0 equiv.) in acetonitrile (6 mL, 0.1 M) at r.t. was added pyrrolidine (260 μ L, 3.17 mmol, 5.0 equiv.). The resultant mixture was stirred at r.t. for 19 h and then filtered through base washed silica. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (5% diethyl ether in petroleum ether) to afford (*Z*)-2,2'-(1-chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[*d*]oxazole) (**8**, 58 mg, 26%) as a yellow solid. R_f = 0.40 (1:9 ethyl acetate:petroleum); IR (CHCl₃) ν (cm⁻¹) 2982, 2882, 1607, 1578, 1549; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.80 – 7.77 (1H, m), 7.56 – 7.54 (1H, m), 7.44 – 7.39 (3H, m), 7.13 (1H, apparent td, J = 7.7, 1.1 Hz), 7.05 (1H, apparent td, J = 7.8, 1.3 Hz), 6.87 (1H, d, J = 7.8 Hz), 3.66 – 3.62 (4H, m), 2.00 – 1.97 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 161.8, 158.1, 150.5, 150.4, 141.9, 141.2, 138.6, 126.1, 124.8, 124.1, 124.0, 120.9, 119.3, 111.1, 109.5, 94.7, 51.3 (2C), 25.6 (2C); HRMS (ESI) m/z : calculated for [M+H]⁺, C₂₀H₁₇ClN₃O₂⁺, 366.1004, found: 366.1000.

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SUPPORTING INFORMATION Tables of reaction parameters examined and copies of ¹H and ¹³C NMR spectra of all newly synthesized products as well as X-ray details of compounds **6e**, **7** and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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