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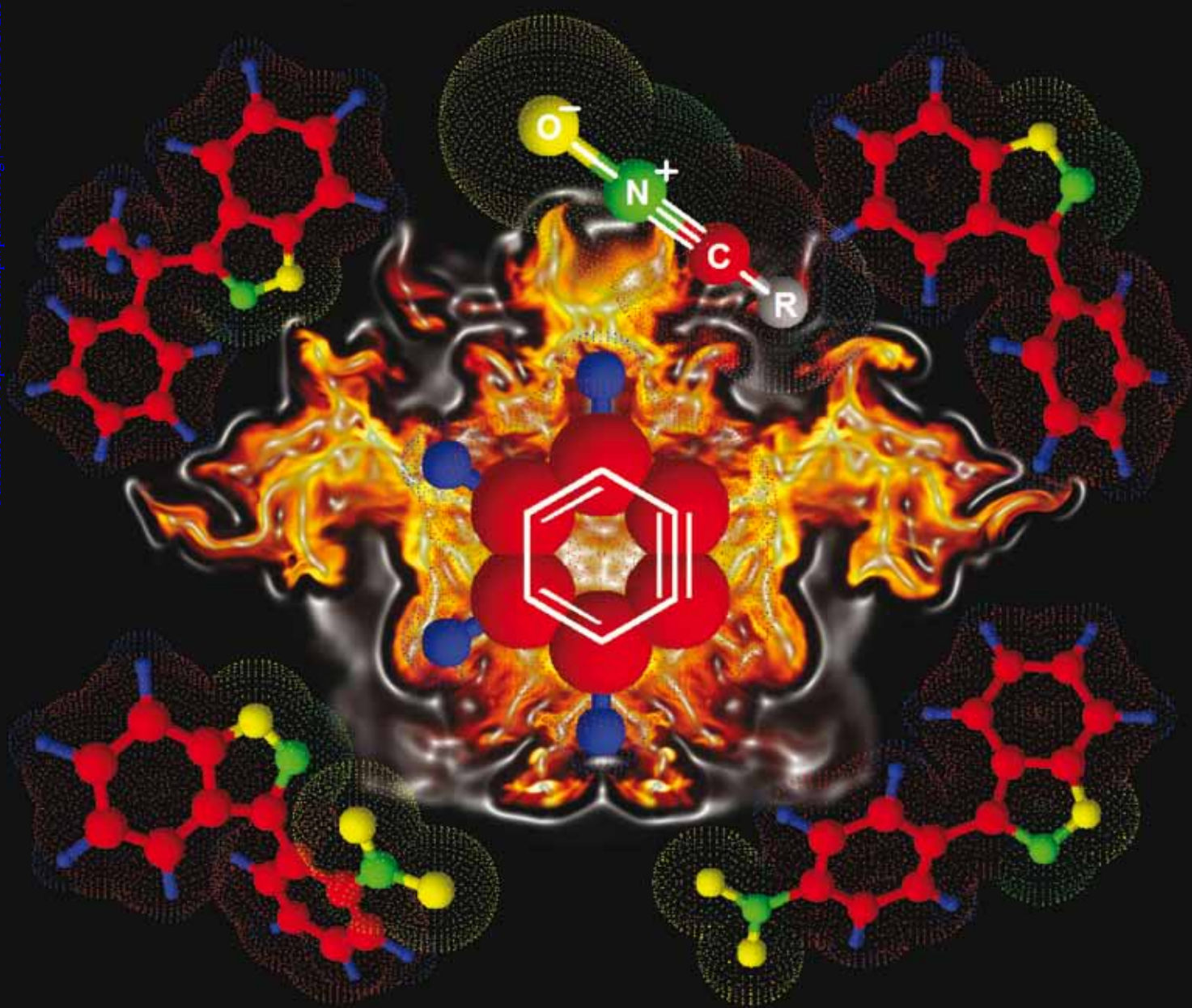
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via 1,3-dipolar cycloaddition of *in situ*
generated nitrile oxides and benzyne

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An efficient entry to 1,2-benzisoxazoles *via* 1,3-dipolar cycloaddition of *in situ* generated nitrile oxides and benzyne†

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An efficient protocol for the synthesis of a range of 1,2-benzisoxazoles using an improved 1,3-dipolar cycloaddition of nitrile oxides and benzyne is described. Key to the procedure is the *in situ* generation of the reactive nitrile oxide and benzyne reactants simultaneously.

Introduction

1,2-Benzisoxazoles are a major class of five membered N–O containing heterocycles with immediate application in the pharmaceutical industry.[1] Their isosteric relationship with the indole core allows 1,2-benzisoxazoles to bind to important biological enzymes in a mode that mimics the indole core.[1g,1i] Consequently, numerous 1,2-benzisoxazoles have been found to possess potent pharmacological properties.[1] This high degree of bioactivity is exemplified by Zonisamide **1**,[1b,1d] a potent antiepileptic drug and the blockbuster drug Risperidone® **2**, approved by the United States FDA in 1993 for the treatment of schizophrenia (Fig. 1).[1a]
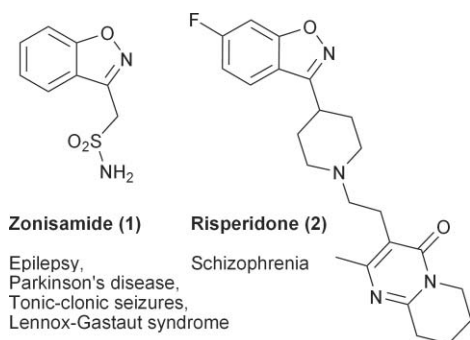

Fig. 1 Example of biologically active 1,2-benzisoxazoles.

Several synthetic methodologies have been developed to access 1,2-benzisoxazoles, driven in part by the desirable biological properties these compounds possess. The most common synthetic routes are illustrated in Scheme 1;[2] (i) formation of the 1-2 bond by an intramolecular cyclization of *o*-hydroxybenzyloxime sulfonates or acetates;[3] (ii) a base-induced intramolecular cyclization of *o*-halo benzoyl derivatives for the formation of the 1-7a bond;[4] (iii) intramolecular oximation for the assembly of
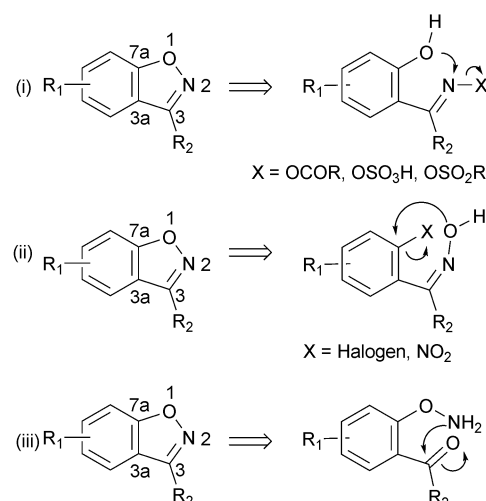
Scheme 1 Synthetic approaches to 1,2-benzisoxazoles.

the 2-3 C=N double bond (although this strategy has been used with less frequency).[5] However, these protocols are often hindered by long reaction times, multiple-steps, and harsh reaction conditions, favoring the formation of undesirable by-products. For example, the basic conditions employed in (i) (Scheme 1) often leads to Beckmann-type rearrangement of the starting material, giving the undesired 1,3-benzisoxazoles.[2] On the other hand, 3-unsubstituted, 3-acyl-, and 3-carboxyl-1,2-benzisoxazoles are easily cleaved in the strongly basic environment used in (i) and (ii), leading to the corresponding salicylonitriles or the salicylic acid derivatives.[2]

An alternative strategy involves the simultaneous formation of the 3-3a and 7a-1 bonds, *via* a Huisgen-type[6] 1,3-dipolar cycloaddition of benzyne (**3**) with nitrile oxides (**4**) (Scheme 2).[4b,7] Unfortunately, such reactions generally suffer from low yields, mainly due to competing side-reaction pathways resulting from the highly reactive intermediates.

Although most attractive in terms of convergence and step-economy, there are limited examples of the syntheses of 1,2-benzisoxazoles using this 1,3-dipolar cycloaddition strategy.[4b,7] One of the earliest applications of this chemistry was reported by Minisci and Quilico (1964) who reacted benzyne (**3**), generated

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† Electronic supplementary information (ESI) available: Experimental data and NMR spectra. See DOI: 10.1039/b927235f

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Org. Biomol. Chem., 2010, **8**, 2537–2542 | 2537
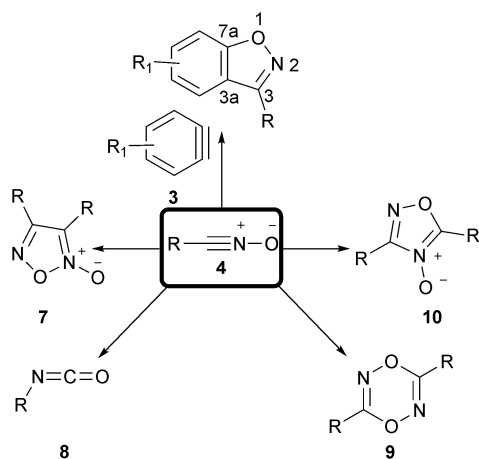
Scheme 2   Reaction pathways of nitrile oxides **4**.

from anthranilic acid (**5**), with benzonitrile oxide to give 3-phenyl-1,2-benzisoxazole (**6**) in 53% yield.[7a] Since these pioneering studies little advance has been made towards a general and reliable method for 1,2-benzisoxazole synthesis using cycloaddition chemistry.[8]

In general, the reactive nitrile oxide species (**4**) are first generated separately, then quickly added to a mixture of benzyne precursor (*e.g.* anthranilic acid (**5**) and an alkyl nitrite). It is not surprising then that side reactions are commonplace, and perhaps this has been a major factor in the limited use of this methodology.

Benzyne (**3**) is an extremely short lived intermediate with an estimated life-time of 400 ps,[9c] undergoing rapid dimerisation *via* a stepwise [2+2] cycloaddition to yield diphenylene.[9a,b] On the other hand, aliphatic and aromatic nitrile oxides dimerize in dilute solutions, even at low temperature (0 °C), within seconds or, at best, minutes to the corresponding furoxans **7** (Scheme 2).[10] The only known stable nitrile oxides are those possessing a highly hindered C≡N⁺–O⁻ group.[11] Furthermore, nitrile oxides are known to isomerize into isocyanates (**8**) at elevated temperatures,[12] while in the presence of pyridine in ethanol or excess BF₃ in benzene, they dimerize furnishing 1,4,2,5-dioxadiazines (**9**).[12] The formation of 1,2,4-oxadiazole-4-oxides (**10**) in the presence of Et₃N or BF₃ is less significant.[13]

Taking into consideration all the available information, it became evident that a substantial improvement of the efficiency of 1,2-benzisoxazole synthesis would only be possible if the relative rates of formation of benzyne (**3**) and nitrile oxide (**4**) were matched. Building upon our recent success in benzyne chemistry, and our emerging interest in developing new protocols for the construction of heterocycles,[14] we were keen to modernise the related nitrile oxide-aryne chemistry.

Arynes are accessible *via* numerous protocols.[15] Until recently, the most widely used involved the diazotization of anthranilic acid derivatives to benzenediazonium-2-carboxylates, which decompose to benzyne (**3**) upon elimination of nitrogen and carbon dioxide.[9a,9b] More recently, arynes have been obtained under milder conditions from *o*-(trimethylsilyl)aryl triflates, *via* fluoride-promoted elimination of the trimethylsilyl group and the *o*-triflate group.[16] In this regard, we have recently reported a one pot protocol to access 1,2-benzisoxazoles utilising *o*-(trimethylsilyl)aryl triflates as the benzyne precursor.[8] However, although preferable in terms of safety and efficiency, this method of benzyne generation

is limited by the availability of starting materials. Anthranilic acids, on the other hand, are widely available with diverse functionality. The 1,3-dipolar nitrile oxides (**4**) are available from their corresponding hydroximoyl chlorides, which upon exposure to a suitable base undergo rapid dehydrodehalogenation.[17]

Herein, we describe an efficient approach to 1,2-benzisoxazoles using a microwave enhanced one-pot protocol, beginning with anthranilic acid (**5**) as a benzyne precursor and hydroximoyl chlorides as a starting point for nitrile oxides (**4**). We believe that this improved method represents a major step forward in the syntheses of 1,2-benzisoxazoles.

Results and discussion

Preliminary studies using anthranilic acid (5) as benzyne precursor

We recently employed anthranilic acid (**5**) as a suitable benzyne precursor in the synthesis of several benzotriazoles. Simply heating **5** in a [1 : 1] ratio with a suitable alkyl nitrite reagent, in the presence of an organic azide, led to the target benzotriazoles in excellent yields.[14] Beginning with these optimised conditions, preliminary investigations were conducted with nitrile oxide precursor, electron rich, *p*-methoxyphenyl hydroximoyl chloride (**11**).

In the initial screening stage the conditions for the formation of benzyne (**3**) were kept constant, while the formation of the nitrile oxide (**4**) was investigated by sampling a range of inorganic and organic bases in polar media. Unfortunately, most conditions did not afford any of the target products,[18] except for the reaction performed on **11** using K₂CO₃ in refluxing MeCN (Scheme 3). These conditions furnished 3-(4-methoxyphenyl)-1,2-benzisoxazole (**12**) in 15% yield. The disappointing results were assumed to be a consequence of an imbalance in the rate of formation of the benzyne (**3**) and nitrile oxide (**4**) intermediates, thus leading to undesirable self-reaction pathways. Indeed, the corresponding furoxan **13** was detected as the main by-product in most instances.[19]
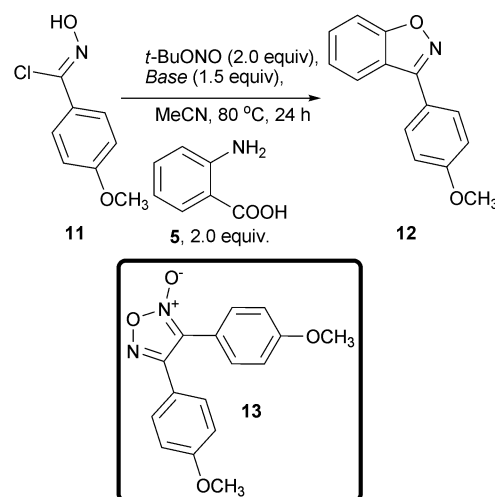
Scheme 3   Successful formation of 1,2-benzisoxazole **12**.

During our previous work on benzotriazoles,[14] we found that microwave irradiation dramatically improved the yield and rate of

Table 1 Optimization

Entry[a]	K$_2$CO$_3$ (equiv.)	Solvent	T (°C)	t (min)	Yield [%][b]
1	1.5	MeCN	120	5	81
2	**1.5**	***MeCN***	**120**	**10**	**85**
3	1.5	MeCN	120	20	74
4	0	MeCN	120	10	—[c]
5	1	MeCN	120	10	74
6	2	MeCN	120	10	73
7	1.5	MeCN	40	10	78
8	1.5	MeCN	80	10	83
9	1.5	MeCN	160	10	81
10	1.5	MeOEt	120	10	63
11	1.5	1,2-DCE	120	10	43
12	1.5	Toluene	120	10	35
13	1.5	THF	120	10	49
14	1.5	MeOH	120	10	3
15	1.5	DMSO	120	10	12
16	1.5	H$_2$O	120	10	27

[a] Reaction performed on 0.54 mmol. [b] Isolated yield. [c] The purification of **12** from by-products was not possible because of similar R$_f$ values.

reaction. Thus when **11** was irradiated at 120 °C in the presence of **5** (2.0 equiv.), *t*-BuONO (2.0 equiv.) and K$_2$CO$_3$ (1.5 equiv.) in MeCN for 10 min **12** was obtained in 85% yield. Keen to build upon this outcome, we endeavoured to optimize the reaction conditions with substrate **11** using K$_2$CO$_3$ as base (Table 1). Surprisingly, we could not improve upon the initial conditions. Firstly, the duration of microwave irradiation was varied, heating the reaction mixture at 120 °C for 5, 10 and 20 min (Table 1, entries 1-3). This did not offer any beneficial effect on the yield of **12**, with longer reaction times showing an erosion of the yield, suggesting degradation of the product under the conditions (Table 1, entry 3).

Next, the number of equivalents of base was investigated by varying the molar ratio of K$_2$CO$_3$ (with respect to **11**) from 0 to 2. The formation of **12** was observed (TLC) even in the absence of base, suggesting that 4-methoxyphenylnitrile oxide was being generated under the given conditions (Table 1, entry 4). In fact, subjecting a solution of **11** in MeCN to microwave conditions (120 °C, 10 min) in the absence of any other reagent, resulted in its consumption (¹H NMR and TLC). Unfortunately, in the absence of K$_2$CO$_3$ the reaction gave numerous by-products which proved difficult to purify by conventional chromatographic techniques. Furthermore, using either 1.0 or 2.0 equivalents of K$_2$CO$_3$ afforded **12** in 74% and 73% isolated yield, respectively (Table 1, entries 5 and 6). Optimal results were obtained using 1.5 equivalents of K$_2$CO$_3$ (Table 1, entry 2). Varying the temperature relative to 120 °C resulted in lower yields of **12** (Table 1, entries 7-9), whereas changing the solvent from MeCN did not offer any benefit (Table 1, entries 10-16).

To explore the scope of this protocol, a variety of hydroximoyl chloride derivatives were examined (Table 2, entries 1-13). In general, good to excellent yields were observed with electron-rich

Table 2 Scope of the reaction

Entry[a]	Product R =	Yield [%][b]
1	**14**	80
2	**15**	96
3	**16**	67
4	**17**	76
5	**18**	71
6	**19**	70
7	**20**	55
8	**21**	90
9	**22**	71
10	**6**	80
11	**23**	39
12	**24**	51
13	**25**	55

[a] Reaction performed on 0.54 mmol of **11**; [b] Isolated yield.

nitrile oxides (Table 2, entries 3, 5, 6 and 8) and/or those having a sterically hindered C≡N⁺–O⁻ group (Table 2, entries 1 and 2). On the other hand, moderate yields were recorded for electron-poor nitrile oxides (Table 2, entries 4, 9 and 13). Pleasingly, 3-phenyl-1,2-benzisoxazole (**6**) was obtained in 80% yield (Table 2, entry 10), almost 30% higher than in the method described by Minisci and Quilico (53%).[7a] This method was found to be amenable to substrates bearing more than one hydroximoyl chloride, as exemplified by **23** (Table 2, entry 11). Gratifyingly, even highly unstable aliphatic nitrile oxides could be used, as demonstrated by **24** (Table 2, entry 12).

Preliminary mechanistic studies

A plausible explanation for the successful results obtained under microwave irradiation was attributed to a possible cycloreversion of an *in situ* generated furoxan to the nitrile oxide (**4**), hence a pool of the reactive intermediate would be stored as the stable furoxan which could be consumed at the rate of benzyne formation. This process is known to occur at elevated temperatures.[20] To test this hypothesis, substrate **11** was subjected to 10 min of microwave irradiation at 120 °C in the presence of K_2CO_3 (1.5 equiv.) in MeCN-d_3 to generate the corresponding furoxan (**13**). ^{1}H NMR of the resulting mixture indicated incomplete consumption of **11**, in addition to numerous other products which we were not able to characterise unequivocally as dimerized material. After allowing the mixture to cool to room temperature, *t*-BuONO and anthranilic acid (**5**) were added, and the heterogeneous mixture was subjected to microwave irradiation at 120 °C for 10 min. The yield, which was under 20%, contradicted the involvement of a dimerized furoxan as the source of the nitrile oxide under our optimised conditions for the synthesis of benzisoxazoles. It was evident that under the microwave "enhanced" conditions, the rate of benzyne (**3**) and nitrile oxide (**4**) formation were tuned to an extent to favour the formation of benzisoxazoles over all other possible side reactions. Interestingly, when a heterogeneous mixture of **11**, **5** (2 equiv.), *t*-BuONO (2 equiv.) and K_2CO_3 (1.5 equiv.) in MeCN were heated at 120 °C in a pressure tube using an oil bath, the corresponding 1,2-benzisoxazole **12** was obtained in 83%. This was comparable to the yield obtained in the microwave reactor, thus excluding any microwave enhancement effect and suggesting the likely involvement of a pressure effect. However, a thorough survey of the reactions, using conventional heating and a sealed tube, was not carried out as the microwave method was more convenient.

Conclusion

In summary, the present protocol describes an expedient one-pot access to 1,2-benzisoxazoles in good to excellent yields from readily accessible starting materials. The reaction was accelerated by using microwave irradiation or heating in a sealed tube, which lead to improved yields compared to previous methods of 1,2-benzisoxazoles synthesis starting from anthranilic acid **5**.

Experimental

General information

Melting points were recorded using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. High Resolution Mass Spectra were recorded on VG micron Autospec or Bruker microTOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin Elmer 1600 series or Bruker Tensor 27 spectrometer as a solution in chloroform. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV(III) 400, Bruker AV 400, Bruker DPX 400 (400 MHz (^{1}H) and 101 MHz (^{13}C)) spectrometers. Coupling constants are given in hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), brd (broad doublet), t (triplet), q (quartet), sept (septet), m (multiplet). Column chromatography was performed

using Merck silica gel 60 (230-400 mesh). All solvents and reagents were used as received from commercial suppliers.

General procedure for the synthesis of 1,2-benzisoxazoles using anthranilic acid 5 as benzyne precursor under microwave conditions—synthesis of 3-(4-methoxyphenyl)-1,2-benzisoxazole (12)

A heterogeneous mixture of 4-methoxyphenylhydroximoyl chloride **11** (100 mg, 0.54 mmol), anthranilic acid **5** (2.0 equiv.), and K_2CO_3 (1.5 equiv.) was stirred in MeCN (2.0 mL) at room temperature for 5 min followed by the addition of *t*-BuONO (2.0 equiv.) in a single portion. The mixture was stirred for an additional 30 s and then heated in a microwave reactor at 120 °C for 10 min. The volatile components were then removed under reduced pressure on a rotatory evaporator at 40 °C. The crude mixture was purified by flash column chromatography on silica gel using 1% ethyl acetate in petroleum ether 40-60 °C as the eluting solvent, giving 3-(4-methoxyphenyl)-1,2-benzisoxazole **12** as a white solid (104 mg, 0.46 mmol, 85%).

3-(4-Methoxyphenyl)-1,2-benzisoxazole (12)

White solid; mp = 100–102 °C (lit.[21] 100–101 °C); IR (v[cm^{-1}]) 3011, 1613; NMR: δ_H (400 MHz, CDCl$_3$) 7.95-7.91 (m, 3H), 7.65-7.56 (m, 2 H), 7.37 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.11-7.09 (m, 1H), 7.08-7.06 (m, 1H), 3.89 (s, 3H); δ_C (100 MHz, CDCl$_3$) 163.7, 161.2, 156.7, 129.6, 129.3 (2C), 123.6, 122.2, 121.1, 120.5, 114.5 (2C), 110.1, 55.3; HRMS (ESI) (*m/z*): [M+H]$^+$ calcd for C$_{14}$H$_{12}$NO$_2$, 226.0863; found 226.0863.

3-(2,6-Dimethylphenyl)-1,2-benzisoxazole (14)

Yellow solid; mp = 85–86 °C (lit.[5] 83–84 °C); IR (v[cm^{-1}]) 3011, 1610; NMR: δ_H (400 MHz, CDCl$_3$) δ 7.70 (td, J = 8.5, 0.8 Hz, 1H), 7.61 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (brd, J = 7.7 Hz, 1H), 7.35-7.29 (m, 2H), 7.20 (brd, J = 7.5 Hz, 2H), 2.15 (s, 6H); δ_C (100 MHz, CDCl$_3$) 163.1, 157.7, 137.7, 129.8, 129.4, 127.6 (2C), 127.1, 123.6, 121.9 (2C), 121.8, 110.0, 20.1 (2C); HRMS (ESI) (*m/z*): [M+H]$^+$ calcd for C$_{15}$H$_{14}$NO, 224.1070; found 224.1075.

3-(2-Ethylphenyl)-1,2-benzisoxazole (15)

Brown oil; IR (v[cm^{-1}]) 2972, 1609; NMR: δ_H (400 MHz, CDCl$_3$) 7.68-7.66 (m, 1H), 7.62-7.59 (m, 2H), 7.52-7.45 (m, 3H), 7.40-7.33 (m, 2H), 2.78 (q, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H); δ_C (100 MHz, CDCl$_3$) 163.0, 158.0, 143.9, 130.2, 130.0, 129.7, 129.4, 127.1, 126.0, 123.7, 122.2 (2C), 109.9, 26.6, 15.8; HRMS (ESI) (*m/z*): [M+H]$^+$ calcd for C$_{15}$H$_{14}$NO, 224.1070; found 224.1069.

3-(2-Methoxyphenyl)-1,2-benzisoxazole (16)

Yellow brown oil; IR (v[cm^{-1}]) 3011, 1610; NMR: δ_H (400 MHz, CDCl$_3$) 7.70 (brd, J = 8.0 Hz, 1H), 7.67 (dd, J = 7.5, 1.7 Hz, 1H), 7.63 (brd, J = 8.4 Hz, 1H), 7.58-7.50 (m, 2H), 7.33-7.29 (m, 1H), 7.14-7.09 (m, 2H), 3.86 (s, 3H); δ_C (100 MHz, CDCl$_3$) 163.2, 157.4, 156.4, 131.6, 131.3, 129.4, 123.5, 123.1, 121.9, 120.9, 117.6, 111.4, 109.7, 55.5; HRMS (ESI) (*m/z*): [M+H]$^+$ calcd for C$_{14}$H$_{12}$NO$_2$, 226.0823; found 226.0864.

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3-(2-Nitrophenyl)-1,2-benzisoxazole (17)

Yellow solid; mp = 105–108 °C; IR (v[cm^{-1}]) 1610, 1532, 1351, 852; NMR: δ_H (400 MHz, CDCl$_3$) 8.22-8.19 (m, 1H), 7.84-7.72 (m, 3H), 7.69-7.67 (m, 1H), 7.64-7.60 (m, 1H), 7.47 (bs, J = 8.0 Hz, 1H), 7.36-7.32 (m, 1H); δ_C (100 MHz, CDCl$_3$) 163.0, 155.7, 148.7, 133.5, 132.2, 131.1, 130.1, 125.0, 124.1, 123.5, 120.9 (2C), 110.15; HRMS (ESI) (m/z): [M+Na]$^+$ calcd for C$_{13}$H$_8$N$_2$NaO$_3$, 263.0427; found 263.0422.

3-(1-Naphthalen)-1,2-benzisoxazole (18)[22]

Orange brown oil; IR (v[cm^{-1}]) 1610; NMR: δ_H (400 MHz, CDCl$_3$) 8.18 (d, J = 8.4 Hz, 1H), 8.06 (brd, J = 8.3 Hz, 1H), 7.98 (brd, J = 7.6 Hz, 1H), 7.82 (dd, J = 7.1, 1.2 Hz, 1H), 7.74 (brd, J = 8.5 Hz, 1H), 7.66-7.51 (m, 5H), 7.35-7.31 (m, 1H); δ_C (100 MHz, CDCl$_3$) 163.3, 157.5, 133.9, 131.3, 130.4, 129.9, 128.4, 128.3, 127.0, 126.4, 125.7, 125.5, 125.2, 123.7, 122.4, 122.3, 110.0; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{17}$H$_{12}$NO, 246.0913; found 246.0907.

3-(2-Naphthalen)-1,2-benzisoxazole (19)

Orange brown oil; IR (v[cm^{-1}]) 1611; NMR: δ_H (400 MHz, CDCl$_3$) 8.48 (s, 1H), 8.12-7.93 (m, 5H), 7.71-7.69 (m, 1H), 7.65-7.58 (m, 3H), 7.45-7.41 (m, 1H); δ_C (100 MHz, CDCl$_3$) 163.9, 157.2, 134.0, 133.2, 129.8, 129.0, 128.5, 127.9 (2C), 127.2, 126.8, 126.4, 125.0, 123.9, 122.3, 120.6, 110.2; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{17}$H$_{12}$NO, 246.0913; found 246.0913.

3-(4-Isopropylphenyl)-1,2-benzisoxazole (20)

Amorphous colourless solid; mp = 78–81 °C; IR (v[cm^{-1}]) 3011, 2966, 1611; NMR: δ_H (400 MHz, CDCl$_3$) 7.96 (td, J = 8.0, 0.9 Hz, 1H), 7.92 (brd, J = 8.3 Hz, 2H), 7.67-7.65 (m, 1H), 7.62-7.58 (m, 1H), 7.44 (brd, J = 8.0 Hz, 2H), 7.38 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 3.02 (sept, J = 7.0 Hz, 1H), 1.33 (d, J = 6.9 Hz, 6H); δ_C (100 MHz, CDCl$_3$) 163.8, 157.2, 151.3, 129.7, 128.1 (2C), 127.2 (2C), 126.4, 123.7, 122.3, 120.6, 110.1, 34.1, 23.9 (2C); HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{16}$H$_{16}$NO, 238.1226; found 238.1230.

3-(4-Biphenyl)-1,2-benzisoxazole (21)

Yellow solid; mp = 116–119 °C (lit.[23] 119–120 °C); IR (v[cm^{-1}]) 1613; NMR: δ_H (400 MHz, CDCl$_3$) 8.09-8.06 (m, 2H), 8.00 (td, J = 8.0, 0.9 Hz, 1H), 7.83-7.80 (m, 2H), 7.70-7.68 (m, 3H), 7.65-7.61 (m, 1H), 7.53-7.48 (m, 2H), 7.44-7.40 (m, 2H); δ_C (100 MHz, CDCl$_3$) 163.8, 156.8, 142.9, 140.1, 129.7, 128.9 (2C), 128.4 (2C), 127.8, 127.7 (3C), 127.1 (2C), 123.8, 122.1, 120.4, 110.1; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{14}$NO, 272.1070; found 272.1077.

3-(3-Bromophenyl)-1,2-benzisoxazole (22)

Pale yellow solid; mp = 86–89 °C (lit.[24] 93–94 °C); IR (v[cm^{-1}]) 1612; NMR: δ_H (400 MHz, CDCl$_3$) 8.15 (d, J = 1.8 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.71-7.63 (m, 3H), 7.49-7.42 (m, 2H); δ_C (100 MHz, CDCl$_3$) 163.9, 156.0, 133.2, 130.9 (2C), 130.6, 130.0, 126.6, 124.1, 123.1, 121.9, 120.0, 110.3; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{13}$H$_9$^{79}BrNO, 273.9862; found 273.9856.

3-(Phenyl)-1,2-benzisoxazole (6)[25]

Off-white solid; mp = 80–83 °C (lit.[26] 80–82 °C); IR (v[cm^{-1}]) 1613; NMR: δ_H (400 MHz, CDCl$_3$) 8.04-7.97 (m, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.66-7.52 (m, 5H), 7.39 (t, J = 7.5 Hz, 1H); δ_C (100 MHz, CDCl$_3$) 163.7, 157.2, 130.1, 129.7, 129.1 (2C), 128.8, 127.9 (2C), 123.8, 122.1, 120.4, 110.0; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{10}$NO, 196.0757; found 196.0762.

1,4-Bis-(1,2-benzisoxazole)benzene (23)

Yellow solid; IR (v[cm^{-1}]) 1611; NMR δ_H (400 MHz, CDCl$_3$) 8.22 (s, 4H), 8.05-8.01 (m, 2H), 7.75-7.71 (m, 2H), 7.69-7.64 (m, 2H), 7.49-7.44 (m, 2H); δ_C (100 MHz, CDCl$_3$) 164.0 (2C), 156.6 (2C), 130.8 (2C), 130.0 (2C), 128.8 (4C), 124.2 (2C), 122.0 (2C), 120.3 (2C), 110.3 (2C); HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{20}$H$_{13}$N$_2$O$_2$ 313.0972, found 313.0978.

3-(1-Phenyl-ethyl)-1,2-benzisoxazole (24)

Colourless oil; IR (v[cm^{-1}]) 2982, 2932, 2855, 1612; NMR: δ_H (400 MHz, CDCl$_3$) 7.47-7.44 (m, 1H), 7.38 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.28-7.22 (m, 4H), 7.20-7.14 (m, 2H), 7.05 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H), 4.46 (q, J = 7.2 Hz, 1H), 1.78 (d, J = 7.2 Hz, 3H); δ_C (100 MHz, CDCl$_3$) 163.2, 161.0, 142.3, 129.5, 128.8 (2C), 127.5 (2C), 127.0, 123.0, 121.9, 121.0, 109.8, 38.0, 20.0; HRMS (ESI) (m/z): [M+Na]$^+$ calcd for C$_{15}$H$_{13}$NNaO, 246.0889; found 246.0912.

3-(4-Nitrophenyl)-1,2-benzisoxazole (25)

Pale yellow solid; mp = 213–214 °C; IR (v[cm^{-1}]) 1607, 1527, 1349, 853; NMR: δ_H (400 MHz, CDCl$_3$) 8.48-8.43 (m, 2H), 8.22-8.18 (m, 2H), 7.98-7.94 (m, 1H), 7.76-7.66 (m, 2H), 7.51-7.46 (m, 1H); δ_C (100 MHz, CDCl$_3$) 164.2, 155.5, 148.8, 135.2, 130.3, 128.9 (2C), 124.6, 124.4 (2C), 121.6, 119.9, 110.5; HRMS (ESI) (m/z): [M+H]$^+$ calcd for C$_{13}$H$_9$N$_2$O$_3$ 241.0608, found 241.0618.

Acknowledgements

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