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Synthesis of Benzisoxazolines by the Coupling of Arynes with Nitrones

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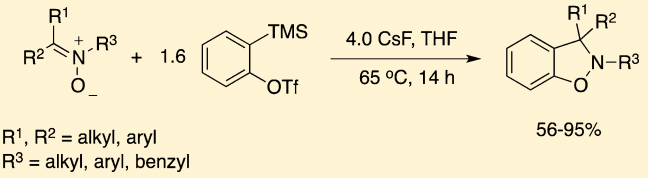
Supporting Information

ABSTRACT: A variety of substituted benzisoxazolines have been synthesized by the [3 + 2] cycloaddition of nitrones and arynes. The reaction scope is broad, the reaction conditions are mild, and the process tolerates a variety of functional groups.



INTRODUCTION

Benzisoxazoline is a critical subunit in pharmaceuticals with important biological and pharmacological activities, including antimicrobial activity against *Salmonella paratyphi*, *Proteus vulgaris*, *Xanthomonas* spp., *Fusarium solanii*, and *Botrytis cinerea*.[1] Benzisoxazolines can also be important synthetic intermediates for the preparation of more complex molecules.[2] Much effort has been devoted to the synthesis of this heterocyclic ring system.[3]

Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported,[4] highly electrophilic arynes have been employed extensively in recent years for the construction of many heteroaromatic structures.[5] Our group has recently reported that simple nucleophilic reactions,[6] annulation reactions,[7] and a variety of 1,3-dipolar cycloadditions[8] provide useful new synthetic routes to a variety of heterocycles, generally affording excellent yields under mild reaction conditions. In a continuation of our work on the reactions of arynes with dipoles, we have investigated the cycloaddition reactions of nitrones and arynes. During this project, related work was communicated by other groups.[9] However, that work generally involved less convenient reaction conditions and aryne precursors, such as *n*-BuLi-promoted halogen exchange of *o*-haloaryl triflates under low temperatures[9b] and $PhI(OAc)_2$/TfOH-promoted generation of benzynes from benzobisoxadisiloles.[9c] More importantly, the authors failed to examine the scope and effect of various functional groups on their processes. Herein, we wish to report our more detailed and extensive results on the 1,3-dipolar cycloaddition reaction of nitrones and arynes generated from *o*-silylaryl triflates to afford a wide variety of substituted benzisoxazolines.[10]

RESULTS AND DISCUSSION

We optimized the reaction conditions for the reaction of the unsubstituted benzyne precursor *o*-(trimethylsilyl)phenyl triflate (**1a**) and *N*-benzylidenebenzylamine *N*-oxide (**2a**) (Table 1). Employing acetonitrile as the solvent and 3.0 equiv of CsF as the fluoride source provides the desired benzisoxazoline **3a** in a 60% yield (Table 1, entry 1). Adding more CsF or more benzyne precursor failed to improve the yield significantly (Table 1, entries 2 and 3). Another fluoride ion source, TBAF,[11] was also examined (Table 1, entries 4 and 5). By utilizing 2.0 equiv of **1a** and 4.0 equiv of TBAF in THF (Table 1, entry 5), a high yield of the corresponding benzisoxazoline (92%) was obtained. These reaction conditions, however, turned out not to be suitable for other nitrones, probably because of the relatively rapid rate of benzyne generation. In order to better control the rate of benzyne generation, differing amounts of CsF in THF were examined, since CsF has limited solubility in THF, thus reducing the rate of benzyne generation (Table 1, entries 6–9). Using 2.0 equiv of **1a** and 5.0 equiv of CsF at 65 °C in THF, a 93% yield of the desired cycloadduct was produced (Table 1, entry 7). Using reduced amounts of the benzyne precursor (1.6 equiv) and CsF (4.0 equiv) still afforded a high 91% yield (Table 1, entry 8).

Using the optimal conditions shown in Table 1, entry 8, the scope and limitations of this methodology have been examined. Various substituted nitrones have been examined in this reaction, and the results are summarized in Table 2.

Excellent yields have been obtained from both *N*-alkyl (Table 2, entries 2–5) and *N*-benzyl-substituted nitrones (Table 2, entries 1 and 6–9). The results suggest that the steric effect of substituents on the carbon of the nitrone double bond are significant. Lower yields are observed for the substrates with more steric hindrance on the carbon of the C–N double bond. For example, **2e**, which has two methyls on the carbon of the C–N double bond (Table 2, entry 5), and **2h**, which has an *ortho*-methoxy-substituted phenyl on that carbon (Table 2, entry 8), both give lower yields. The process has also been applied to *N*-aryl-substituted nitrone **2j** (Table 2, entry 10), which affords a high 92% yield of benzisoxazoline **3j**.

Nitrones with a variety of functionally substituted phenyl groups on the nitrone carbon have been examined under our optimal conditions (Table 2, entries 11–19). Many functional groups are well tolerated, including ester, cyano, amino, halogen, and other groups. Nitrones with electron-donating

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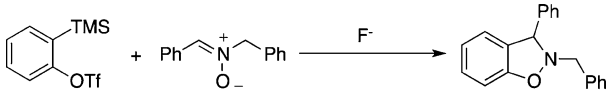
Table 1. Optimization Studies of the Reaction between *o*-(Trimethylsilyl)phenyl Triflate (1a) and *N*-Benzylidenebenzylamine *N*-Oxide (2a)[a]



1a 2a 3a

entry	benzyne (equiv)	CsF (equiv)	solvent	temp (°C)	time (h)	% yield of 3a[b]
1	1.2	3.0	MeCN	rt	24	60
2	1.2	4.0	MeCN	rt	24	65
3	2.0	3.0	MeCN	rt	24	56
4	1.2	2.0 TBAF[c]	THF	rt	24	45
5	2.0	4.0 TBAF[c]	THF	45	24	92
6	1.2	3.0	THF	65	24	68
7	2.0	5.0	THF	65	14	93
8	1.6	4.0	THF	65	14	91
9	1.6	3.0	THF	65	24	83

[a]All reactions were conducted on a 0.25 mmol scale in 5 mL of solvent for 24 h. [b]Yields of products isolated by column chromatography. [c]1 M TBAF in THF solution.

groups tend to result in lower yields (Table 2, entries 15 and 16) than nitrones with electron-withdrawing groups (Table 2, entries 11−14), presumably because of the reduced electrophilicity of the carbon−nitrogen double bond due to the presence of such groups (see the later mechanistic discussion). Nitrone **2q** also afforded a relatively low yield of 57%, mainly because of the steric hindrance produced by the *ortho*-methoxy group (Table 2, entry 17). Because of the presence of the additional carbon−carbon double bond in **2s**, the reaction was not as clean as that of other substrates but still produced a good yield (Table 2, entry 19).[12] Several cyclic nitrones have also been examined, and moderate yields have been obtained (Table 2, entries 21−23).

After a variety of substituted nitrones were examined, the behavior of various aryne precursors was studied in this reaction (Table 3).

Symmetrical dimethyl- (**1b**), dimethoxy- (**1c**), and difluoro-substituted (**1d**) benzyne precursors have been employed under our optimal reaction conditions with nitrone **2f**. All of these substrates generated comparable but lower yields than benzyne itself. Similar results have been observed before in other reaction systems.[6] The unsymmetrical methoxy-substituted benzyne precursor **1e** provided benzisoxazoline **3fe** as a single regioisomer in a 75% yield. Two possible mechanisms for this process are proposed in Scheme 1 on the basis of the experimental results and previous experience.[8]

Following the formation of benzyne induced by fluoride from benzyne precursor **1e**, a [3 + 2] cycloaddition can occur. Nucleophilic attack of the oxygen anion of **2f** on benzyne, quickly followed by cyclization of **3fe′**, can be envisioned as a mechanistic alternative. The significant steric and electronic effects of the substituents on the carbon−nitrogen double bond of the nitrone on the reaction results are consistent with both of these proposed mechanisms. The steric hindrance arising from the substituent on the carbon of the C−N double bond (see the results of entries 5, 8, and 17 in Table 2) is expected to disfavor the cycloaddition of **2f** to **3fe** or the cycloaddition of **3fe′** to **3fe**. Furthermore, the presence of electron-withdrawing substituents on the phenyl group present on the carbon of the C−N double bond (see the results of entries 12−16 in Table 2) would be expected to increase the electrophilicity of the C−N double bond in **3fe′**, producing higher yields of the products.

CONCLUSIONS

In conclusion, we have developed a facile and general method for the synthesis of substituted benzisoxazolines by the 1,3-dipolar cycloaddition of arynes and nitrones under mild reaction conditions, which provides excellent yields. A variety of functional groups are well tolerated in this process, allowing further synthesis of more complicated molecules.

EXPERIMENTAL SECTION

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. All melting points are uncorrected. High resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (SiO_2, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **1a**, CsF, TBAF solution (1 M in THF), and acetonitrile were purchased from Sigma-Aldrich. 4,5-Dimethyl-substituted silylaryl triflate **1b**, 4,5-dimethoxy-substituted silylaryl triflate **1c** and 4,5-difluoro-substituted silylaryl triflate **1d** were prepared according to a literature procedure.[13]

Noncommercially Available Compounds. Noncommercially available starting materials were prepared according to literature procedures.[14]

*(2-Methoxyphenylmethylene)benzylamine-N-oxide (**2h**).* Light yellow solid: mp 78−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (dd, J = 7.8, 1.5 Hz, 1H), 7.96 (s, 1H), 7.51−7.26 (m, 7H), 6.99 (t, J = 8.1 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 133.9, 131.7, 129.1, 128.9, 128.8, 128.8, 120.8, 119.7, 109.8, 71.7, 55.6; HRMS (EI) calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1101.

*(3-Nitrophenylmethylene)benzylamine-N-oxide (**2i**).* Yellow solid: mp 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.57 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.57−7.41 (m, 7H), 5.11 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 133.8, 132.8, 132.1, 132.0, 129.6, 129.5, 129.5, 129.2, 124.7, 123.1, 71.9; HRMS (EI) calcd for $C_{14}H_{12}N_2O_3$ 256.0848, found 256.0843.

*(5-Bromo-2-methoxyphenylmethylene)phenylamine-N-oxide (**2q**).* Yellow solid: mp 135−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J = 2.7 Hz, 1H), 8.33 (s, 1H), 7.78−7.74 (m, 2H), 7.51−7.46 (m, 4H), 6.79 (d, J = 9.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 149.6, 134.6, 131.1, 130.1, 129.3, 128.2, 121.9, 121.7, 113.6, 111.7, 56.1; HRMS (EI) calcd for $C_{14}H_{12}NO_2Br$ 305.0051, found 305.0049.

*(4,5-Dimethoxy-3-iodophenylmethylene)phenylamine-N-oxide (**2r**).* Yellow solid: mp 162−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ

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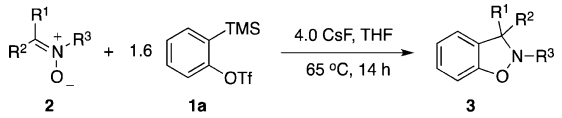
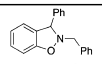
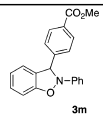
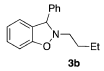
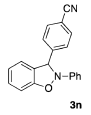
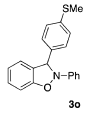
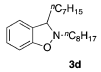
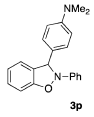
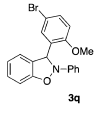
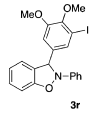
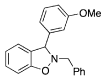
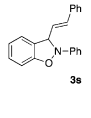
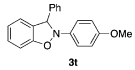
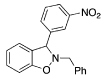
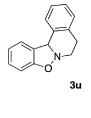
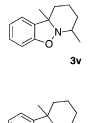
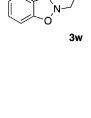
Table 2. Cycloadditions of Benzyne with Nitrones[a]

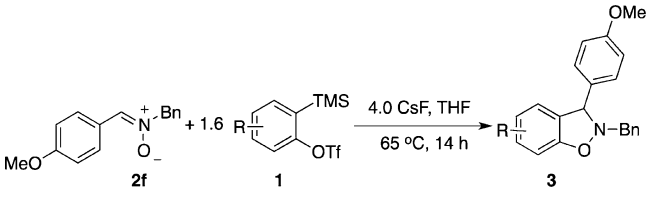


2 1a 3

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	 3a	91	13	 3m	90
2	 3b	88	14	 3n	88
3	 3c	95	15	 3o	77
4	 3d	90	16	 3p	74
5	 3e	79	17	 3q	57
6	 3f	90	18	 3r	70
7	 3g	79	19	 3s	56
8	 3h	65	20	 3t	64
9	 3i	69	21	 3u	65
10	 3j	92	22	 3v	60
11	 3k	90	23	 3w	64
12	 3l	93			

[a]Unless otherwise stated, all reactions have been carried out on a 0.25 mmol scale, with 1.6 equiv of benzyne precursor **1a** and 4.0 equiv of CsF in 5 mL of THF at 65 °C for 14 h. [b]Yields of products isolated by column chromatography.

Table 3. Investigation of Different Arynes in the Coupling Reaction with Nitrone 2f[a]



2f 1 3

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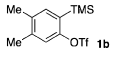
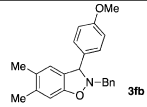
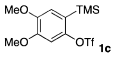
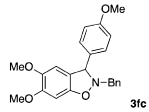
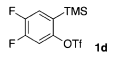
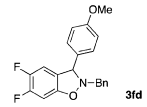
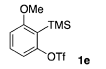
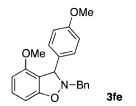
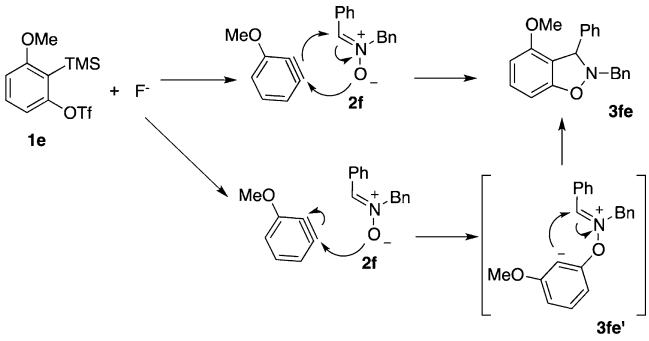
1	 1b	 3fb	72
2	 1c	 3fc	70
3	 1d	 3fd	41
4	 1e	 3fe	75

[a]Unless otherwise stated, all reactions have been carried out on a 0.25 mmol scale, with 1.6 equiv of benzyne precursor **1a** and 4.0 equiv of CsF in 5 mL of THF at 65 °C for 14 h. [b]Yields of products isolated by column chromatography.

Scheme 1. Possible Mechanisms



8.60 (d, J = 1.5 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.82 (s, 1H), 7.75–7.72 (m, 2H), 7.45 (m, 3H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 150.8, 148.9, 132.8, 132.3, 130.2, 129.3, 128.8, 121.7, 112.5, 92.0, 60.7, 56.1; HRMS (EI) calcd for $C_{15}H_{14}NO_3I$ 383.0018, found 383.0014.

Representative Procedure for the Cycloaddition of Arynes and Nitrones. An oven-dried 6-dram vial equipped with a stir bar was charged with 0.25 mmol of the nitrone, 0.40 mmol (1.6 equiv) of the aryne precursor, and 1.00 mmol (152 mg, 4.0 equiv) of CsF, followed by 5 mL of dry THF. The vial was sealed and placed in an oil bath at 65 °C for about 14 h. The resulting mixture was cooled and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with ethyl acetate/hexanes or dichloromethane/hexane as the eluent.

*2-Benzyl-3-phenyl-2,3-dihydrobenzo[d]isoxazole (**3a**).* White solid (65.5 mg, 91%): mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 2H), 7.39–7.28 (m, 8H), 7.23 (t, J = 7.7 Hz, 1H), 7.04 (d, J

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= 7.5 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 4.41 (d, *J* = 13.3 Hz, 1H), 4.18 (d, *J* = 13.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 140.7, 136.6, 129.5, 129.1, 129.0, 128.8, 128.7, 128.2, 128.0, 127.9, 124.5, 121.7, 117.6, 108.4, 72.9, 63.0; HRMS (EI) calcd for $C_{20}H_{17}NO$ 287.1310, found 287.1304.

2-Butyl-3-phenyl-2,3-dihydrobenzo[d]isoxazole (**3b**). Colorless oil (55.7 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.33 (m, 5H), 7.22 (t, *J* = 6.0 Hz, 1H), 7.00 (d, *J* = 6.0 Hz, 1H), 6.93−6.87 (m, 2H), 3.27 (m, 1H), 3.01 (m, 1H), 1.78−1.71 (m, 2H), 1.51−1.38 (m, 2H), 0.95 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 140.8, 129.5, 129.0, 128.1, 128.0, 124.1, 121.3, 108.0, 74.5, 59.6, 30.0, 20.6, 14.1; HRMS (EI) calcd for $C_{17}H_{19}NO$ 253.1467, found 253.1463.

2-tert-Butyl-3-phenyl-2,3-dihydrobenzo[d]isoxazole (**3c**). White solid (60.2 mg, 95%): mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5H), 7.14 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 6.0 Hz, 1H), 6.83−6.79 (m, 2H), 5.61 (s, 1H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 144.1, 130.0, 128.8, 127.6, 127.5, 123.8, 120.9, 106.9, 67.2, 61.2, 29.9, 25.7; HRMS (EI) calcd for $C_{17}H_{19}NO$ 253.1467, found 253.1468.

2-Octyl-3-heptyl-2,3-dihydrobenzo[d]isoxazole (**3d**). Colorless oil (74.8 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.09 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.09 (dd, *J* = 7.7, 5.3 Hz, 1H), 3.02 (dd, *J* = 13.2, 6.5 Hz, 1H), 2.79−2.58 (m, 1H), 1.70−1.66 (m, 4H), 1.49−1.17 (m, 20H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 129.3, 128.6, 123.9, 121.1, 108.4, 70.0, 60.4, 36.8, 32.1, 29.8, 29.7, 29.5, 29.5, 27.8, 27.6, 26.0, 22.9, 14.3; HRMS (EI) calcd for $C_{22}H_{37}NO$ 331.2875, found 331.2878.

2-Isopropyl-3,3-dimethyl-2,3-dihydrobenzo[d]isoxazole (**3e**). Light brown oil (37.6 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.15 (m, 2H), 6.92 (t, *J* = 6.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 4.05 (t, *J* = 6.0 Hz, 1H), 3.03 (m, 1H), 2.68 (m, 1H), 1.71 (m, 4H), 1.01 (td, *J* = 9.0, 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 129.0, 128.7, 123.9, 121.1, 108.3, 71.2, 62.3, 29.5, 21.0, 12.0, 10.3; HRMS (EI) calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1308.

2-Benzyl-3-(4-methoxyphenyl)-2,3-dihydrobenzo[d]isoxazole (**3f**). White solid (71.2 mg, 90%): mp 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.31 (m, 5H), 7.26−7.20 (m, 3H), 7.02 (d, *J* = 6.0 Hz, 1H), 6.95−6.86 (m, 4H), 5.34 (s, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 156.4, 136.7, 132.6, 129.5, 129.2, 129.2, 129.0, 128.6, 127.8, 124.3, 121.6, 114.2, 108.3, 72.5, 62.6, 55.5; HRMS (EI) calcd for $C_{21}H_{19}NO_2$ 317.1416, found 317.1420.

2-Benzyl-3-(3-methoxyphenyl)-2,3-dihydrobenzo[d]isoxazole (**3g**). White solid (63.0 mg, 79%): mp 69−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.0 Hz, 2H), 7.41−7.32 (m, 3H), 7.83 (m, 2H), 7.29−7.21 (m, 2H), 7.07 (d, *J* = 6.0 Hz, 1H), 6.96−6.83 (m, 5H), 5.36 (s, 3H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 156.3, 142.2, 136.5, 129.8, 129.5, 129.1, 128.8, 128.6, 127.9, 124.4, 121.6, 120.2, 113.8, 113.3, 108.3, 72.7, 62.9, 55.4; HRMS (EI) calcd for $C_{21}H_{19}NO_2$ 317.1416, found 317.1422.

2-Benzyl-3-(2-methoxyphenyl)-2,3-dihydrobenzo[d]isoxazole (**3h**). White solid (51.8 mg, 65%): mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.0 Hz, 2H), 7.38−7.19 (m, 8H), 6.95−6.86 (m, 4H), 5.89 (s, 1H), 4.37 (d, *J* = 15.0 Hz, 1H), 4.18 (d, *J* = 15.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 156.4, 137.1, 129.6, 129.4, 128.9, 128.9, 128.5, 127.6, 124.8, 121.6, 121.1, 110.4, 108.5, 66.4, 63.5, 55.5; HRMS (EI) calcd for $C_{21}H_{19}NO_2$ 317.1416, found 317.1419.

2-Benzyl-3-(3-nitrophenyl)-2,3-dihydrobenzo[d]isoxazole (**3i**). White solid (57.1 mg, 69%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.62 (d, *J* = 6.0 Hz, 2H), 7.49−7.25 (m, 8H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 5.44 (s, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.13 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 148.1, 143.3, 135.7, 133.7, 129.8, 129.8, 129.6, 128.8, 128.2, 127.3, 124.4, 123.0, 122.6, 122.1, 108.8, 71.5, 63.2; HRMS (EI) calcd for $C_{20}H_{16}N_2O_3$ 332.1161, found 332.1166.

2,3-Diphenyl-2,3-dihydrobenzo[d]isoxazole (**3j**). Light brown oil (62.7 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.15 (m, 2H), 7.09−6.85 (m, 7H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.62 (t, *J* = 6.0 Hz, 1H), 6.53−6.49 (m, 1H), 6.43 (dd, *J* = 6.0, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 138.6, 136.5, 131.5, 129.9, 129.5, 129.1, 127.7, 127.2, 122.8, 121.1, 118.3, 110.2, 108.9, 99.3; HRMS (EI) calcd for $C_{19}H_{15}NO$ 273.1154, found 273.1152.

3-(2-Chlorophenyl)-2-phenyl-2,3-dihydrobenzo[d]isoxazole (**3k**). White solid (69.2 mg, 90%): mp 74−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.0 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.29−7.15 (m, 5H), 7.08 (dt, *J* = 9.0, 3.0 Hz, 2H), 6.99 (t, *J* = 9.0 Hz, 1H), 6.92−6.87 (m, 1H), 6.82−6.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 142.3, 135.3, 134.4, 133.5, 131.0, 130.3, 129.6, 128.8, 127.6, 122.7, 121.4, 121.3, 117.5, 110.5, 109.2, 95.6; HRMS (EI) calcd for $C_{19}H_{14}NOCl$ 307.0764, found 307.0769.

2-Phenyl-3-(4-trifluoromethylphenyl)-2,3-dihydrobenzo[d]-isoxazole (**3l**). White solid (79.4 mg, 93%): mp 86−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, *J* = 9.6 Hz, 4H), 7.32−7.24 (m, 2H), 7.13−7.01 (m, 4H), 6.94−6.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 142.6, 142.4, 134.6, 129.8, 127.7, 126.2, 126.2, 126.1, 126.1, 123.3, 121.6, 118.4, 110.8, 109.1, 98.4; HRMS (EI) calcd for $C_{20}H_{14}NOF_3$ 341.1027, found 341.1032.

3-(4-Carbomethoxyphenyl)-2-phenyl-2,3-dihydrobenzo[d]-isoxazole (**3m**). White solid (74.2 mg, 90%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.10 (m, 3H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.92−6.79 (m, 4H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 150.5, 143.1, 142.5, 134.7, 131.5, 130.4, 129.7, 127.3, 123.2, 121.5, 121.4, 118.5, 110.5, 109.0, 98.6, 52.4; HRMS (EI) calcd for $C_{21}H_{17}NO_3$ 331.1208, found 331.1215.

3-(4-Cyanophenyl)-2-phenyl-2,3-dihydrobenzo[d]isoxazole (**3n**). White solid (65.7 mg, 88%): mp 105−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.65 (m, 4H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.12−7.03 (m, 4H), 6.94−6.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 143.5, 133.0, 129.8, 128.0, 123.5, 121.7, 121.7, 118.6, 118.5, 113.7, 111.0, 109.2, 98.2; HRMS (EI) calcd for $C_{20}H_{14}N_2O$ 298.1106, found 298.1106.

3-(4-Methylthiophenyl)-2-phenyl-2,3-dihydrobenzo[d]isoxazole (**3o**). White solid (61.8 mg, 77%): mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 9.0 Hz, 2H), 7.29−7.23 (m, 4H), 7.12−7.08 (m, 3H), 7.00 (t, *J* = 9.0 Hz, 1H), 6.90−6.83 (m, 1H), 6.80−6.76 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 142.5, 140.8, 135.2, 130.2, 129.6, 127.7, 126.7, 122.8, 121.2, 121.1, 118.4, 110.1, 108.9, 98.9, 15.7; HRMS (EI) calcd for $C_{20}H_{17}NOS$ 319.1031, found 319.1034.

3-[4-(Dimethylamino)phenyl]-2-phenyl-2,3-dihydrobenzo[d]-isoxazole (**3p**). Light brown oil (58.3 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.29−7.20 (m, 3H), 7.16−7.08 (m, 3H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.86 (td, *J* = 6.0, 3.0 Hz, 1H), 6.79−6.77 (m, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 150.7, 142.5, 129.6, 129.4, 128.4, 125.8, 122.5, 120.9, 120.7, 118.4, 112.4, 109.6, 108.7, 99.6, 40.6; HRMS (EI) calcd for $C_{21}H_{20}ON_2$ 316.1576, found 316.1583.

3-(5-Bromo-2-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[d]-isoxazole (**3q**). White solid (54.6 mg, 57%): mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.0 Hz, 1H), 7.43 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.27 (t, *J* = 6.0 Hz, 2H), 7.19−7.16 (m, 2H), 7.11−7.08 (dd, *J* = 9.0, 3.0 Hz, 2H), 7.00 (t, *J* = 9.0 Hz, 1H), 6.90 (td, *J* = 6.0, 3.0 Hz, 1H), 6.85 (s, 1H), 6.80 (dd, *J* = 9.0, 3.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.5, 142.8, 134.3, 133.7, 130.8, 129.6, 128.4, 122.6, 121.4, 121.2, 117.4, 113.5, 113.2, 111.0, 109.1, 93.4, 56.3; HRMS (EI) calcd for $C_{20}H_{16}NO_2Br$ 381.0364, found 381.0368.

3-(4,5-Dimethoxy-3-iodophenyl)-2-phenyl-2,3-dihydrobenzo[d]-isoxazole (**3r**). Light brown oil (80.3 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.0 Hz, 1H), 7.33 (d, *J* = 6.0 Hz, 2H), 7.16−7.05 (m, 6H), 6.93 (td, *J* = 9.0, 6.0 Hz, 1H), 6.83 (t, *J* = 6.0 Hz, 2H), 6.70 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 150.3, 150.2, 142.6, 136.3, 134.8, 129.7, 129.5, 123.3, 121.4, 118.6, 111.4, 110.6, 109.0, 98.4, 92.9, 60.6, 56.2; HRMS (EI) calcd for $C_{21}H_{18}NO_3I$ 459.0331, found 459.0320.

2-Phenyl-3-(E-2-phenylethenyl)-2,3-dihydrobenzo[d]isoxazole (**3s**). Light brown oil (42.1 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ

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7.48−7.43 (m, 3H), 7.38−7.28 (m, 6H), 7.09−7.05 (m, 2H), 6.92−6.72 (m, 4H), 6.48−6.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 142.8, 135.3, 131.5, 129.6, 129.3, 128.8, 128.7, 127.3, 125.4, 122.9, 121.2, 121.1, 118.5, 110.8, 108.9, 99.1; HRMS (EI) calcd for $C_{21}H_{17}ON$ 299.1310, found 299.1305.

*2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydrobenzo[d]isoxazole (**3t**).* White solid (48.6 mg, 64%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.0, 3.0 Hz, 2H), 7.36 (t, J = 3.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 2H), 6.82−6.74 (m, 6H), 6.64 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 150.4, 138.6, 136.9, 135.6, 129.9, 128.9, 127.6, 122.6, 121.3, 120.3, 114.8, 108.9, 108.4, 100.5, 55.6; HRMS (EI) calcd for $C_{20}H_{17}NO_2$ 303.1259, found 303.1255.

*5,12-Dihydro-6H-[1,2]benzisoxazolo[3,2]isoquinoline (**3u**).* White solid (36.4 mg, 65%): mp 69−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 9.0 Hz, 1H), 7.29 (t, J = 9.0 Hz, 1H), 7.22−7.09 (m, 4H), 6.90−6.83 (m, 2H), 5.80 (s, 1H), 3.36−3.30 (m, 2H), 3.00−2.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 134.1, 133.5, 129.1, 128.8, 128.6, 127.2, 127.0, 126.9, 123.6, 121.6, 108.7, 65.7, 49.9, 26.9; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1003.

*7,10a-Dimethylpyrido-8,9,10-trihydro[1,2]benzisoxazole (**3v**).* Colorless oil (30.5 mg, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, J = 6.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 6.87 (t, J = 6.0 Hz, 1H), 6.78 (d, J = 9.0 Hz, 1H), 3.22 (m, 1H), 1.63−1.51 (m, 9H), 1.41 (d, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 136.9, 128.0, 121.0, 120.8, 108.0, 65.6, 54.0, 33.3, 26.3, 22.8, 20.3, 19.3; HRMS (EI) calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1306.

*10a-Methyl-7,8,9,10-tetrahydropyrido[1,2]benzisoxazole (**3w**).* Colorless oil (30.4 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 6.0 Hz, 1H), 6.97 (t, J = 6.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 3.39 (m, 1H), 2.64 (td, J = 9.0, 6.0 Hz, 1H), 2.29 (m, 1H), 1.86 (m, 1H), 1.65−1.51 (m, 3H), 1.35 (s, 3H), 1.35−1.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 133.4, 128.2, 121.8, 121.7, 110.0, 67.0, 52.7, 32.8, 30.0, 23.5, 20.5; HRMS (EI) calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1149.

*2-Benzyl-3-(4-methoxyphenyl)-2,3-dihydro-5,6-dimethylbenzo-[d]isoxazole (**3fb**).* Yellow solid (62.0 mg, 72%): mp 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5H), 7.18 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.78 (s, 1H), 6.68 (s, 1H), 5.25 (s, 1H), 4.35 (d, J = 13.0 Hz, 1H), 4.12 (d, J = 13.0 Hz, 1H), 3.79 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 154.8, 137.5, 136.8, 133.2, 129.7, 129.6, 129.5, 129.1, 128.6, 127.7, 126.5, 125.1, 114.1, 109.3, 72.3, 62.8, 55.5, 20.5, 19.6; HRMS (EI) calcd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1721.

*2-Benzyl-5,6-dimethoxy-3-(4-methoxyphenyl)-2,3-dihydrobenzo-[d]isoxazole (**3fc**).* Light brown oil (66.2 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.27 (m, 5H), 7.16 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 6.53 (d, J = 9.0 Hz, 2H), 5.27 (s, 1H), 4.35 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 15.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 150.8, 150.3, 144.5, 136.8, 132.8, 129.5, 129.4, 128.6, 127.8, 118.7, 114.2, 107.9, 93.6, 73.0, 62.8, 57.0, 56.4, 55.5; HRMS (EI) calcd for $C_{23}H_{23}NO_4$ 377.1627, found 377.1620.

*2-Benzyl-5,6-difluoro-3-(4-methoxyphenyl)-2,3-dihydrobenzo[d]-isoxazole (**3fd**).* Light brown oil (36.3 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.31 (m, 6H), 7.20 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.77 (t, J = 9.0 Hz, 1H), 6.66 (dd, J = 9.0, 6.0 Hz, 1H), 5.27 (s, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.16 (d, J = 12.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 136.2, 129.4, 129.3, 128.7, 128.0, 114.4, 112.7, 112.4, 98.3, 98.0, 72.5, 62.5, 55.5; HRMS (EI) calcd for $C_{21}H_{17}NO_2F_2$ 353.1227, found 353.1230.

*2-Benzyl-4-methoxy-3-(4-methoxyphenyl)-2,3-dihydrobenzo[d]-isoxazole (**3fe**).* Colorless oil (64.8 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J = 7.0 Hz, 2H), 7.36 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 5.37 (s, 1H), 4.39 (d, J = 12.8 Hz, 1H), 4.05 (d, J = 12.9 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 157.9, 156.6, 136.3, 132.9, 130.4, 129.5, 128.5, 128.4, 127.7, 115.1, 113.7, 104.1, 101.8, 69.3, 63.0, 55.5, 55.2; HRMS (EI) calcd for $C_{22}H_{21}NO_3$ 347.1521, found 347.1521. Note: In the 1D-NOE experiment, a correlation of 5.37 (s, 1H) to 3.75 (s, 3H). but not to 6.57 (d, J = 8.0 Hz, 1H) or 6.51 (d, J = 8.2 Hz, 1H), is observed. This would not be the case if the compound **3fe** were the other regioisomer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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