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Synthesis of Dihydrobenzisoxazoles by the [3+2] Cycloaddition of Arynes and Oxaziridines

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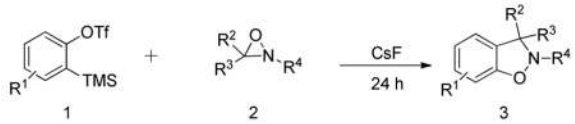
Abstract



R^1 = H, Me, F, *etc.* R^2 = aryl, heteroaryl, alkyl, naphthyl, *etc.*
R^3 = H, alkyl
R^4 = alkyl

Dihydrobenzisoxazoles are readily prepared in good yields by the [3+2] cycloaddition of oxaziridines and arynes. The reaction involves an unusual cleavage of the C-O bond of the oxaziridine and tolerates a variety of substituents on the oxaziridine and the *o*-(trimethylsilyl)aryl triflate to form aryl-, heteroaryl-, alkyl- and naphthyl-substituted dihydrobenzisoxazoles. The resulting halogen-substituted dihydrobenzisoxazoles are readily elaborated to more complex products using palladium-catalyzed crossing-coupling processes.

Introduction

For decades, an intense research effort has been devoted to the synthesis of biologically and pharmaceutically important heterocyclic compounds. However, there are relatively few methods to synthesize dihydrobenzisoxazoles, which appear to have considerable pharmaceutical promise.[1] Recently, the reactions of oxaziridines[2] bearing a three-membered strained heterocyclic ring and alkynes[3] or alkenes[4] have been reported to produce isoxazolines and isoxazolidines respectively by a [3+2] cycloaddition involving C-O bond cleavage. Since arynes are generally more reactive than alkynes and alkenes,[5] we hypothesized that arynes, which are readily prepared *in situ* from *o*-(trimethylsilyl)aryl triflates,[6] and oxaziridines might provide a novel synthetic route to synthesize dihydrobenzisoxazoles under mild reaction conditions.

Oxaziridines consisting of a nitrogen, oxygen and carbon in a three-membered ring exhibit unusually high reactivity, because of the inherently weak N-O bond.[7] Oxaziridines have been used as both oxygenating and aminating agents for enolates,[8] alkenes,[9] nitrogen nucleophiles[10] and C-H bonds.[11] In addition, oxaziridines undergo some useful rearrangements with low-valent metals[12] and cycloaddition reactions with a variety of heterocumulenes to form a very diverse set of five-membered ring heterocycles.[13] The

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Supporting Information Available
Characterization of the new oxaziridines and dihydrobenzisoxazole final products, including full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the internet at http://pubs.acs.org.

mechanism of these reactions appears to involve nucleophilic attack on the oxaziridine nitrogen with N-O or C-N bond cleavage.

Highly reactive arynes have been extensively used for the preparation of a wide range of aromatic heterocycles.[14–16] Many biologically important heterocycles have been obtained from arynes by Pd-catalyzed annulation reactions,[17] electrophilic and nucleophilic reactions,[18] inter- or intramolecular cycloaddition reactions,[19] and insertion reactions.[20] In our previous studies, we have reported the synthesis of benzotriazoles,[21] indazoles[22] and benzisoxazoles[23] by the [3+2] cycloaddition reaction of azides, diazo compounds and nitrile oxides with arynes respectively. We now wish to report the synthesis of dihydrobenzisoxazoles by the [3+2] cycloaddition of arynes and oxaziridines.

Results and Discussion

First, a number of oxaziridines have been prepared from the corresponding aldehydes and amines, followed by oxidation. A simple method for the preparation of oxaziridines involves the oxidation of imines by *m*-chloroperoxybenzoic acid (*m*-CPBA).[2,24] Using this approach, a variety of aromatic, aliphatic, heterocyclic and polycyclic oxaziridines have been synthesized as mixtures of diastereoisomers (Table 1).[25] We have focused our efforts on the synthesis of only more thermally stable oxaziridines. For instance, more stable *N*-*tert*-butyl oxaziridines[26] are readily prepared from *t*-butyl amine and aromatic aldehydes, followed by oxidation.

Optimization of the cycloaddition

The reaction of *o*-(trimethylsilyl)phenyl triflate (**1a**) with 2-*tert*-butyl-3-phenyl-1,2-oxaziridine (**2a**) and CsF was optimized (Table 2). Benzyne precursor **1a** was allowed to react with **2a** and 3 equiv of CsF for 24 h at room temperature, but the starting oxaziridine **2a** was recovered (entry 1). A trace amount of the desired product **3aa** was formed when the temperature was increased to 65 °C in acetonitrile (entry 2). Thus, elevated temperatures were used for all subsequent cycloaddition reactions of **1a** and **2a**. The desired product was obtained in 59% yield by using dimethoxyethane (DME) as the solvent at 90 °C (entry 3). Not only a much lower yield, but also decomposition of the starting compounds was observed when the reaction was run in toluene or dimethylformamide (DMF) at 120 °C for 24 h (entries 4 and 5). A yield of 77% of **3aa** was observed when *o*-(trimethylsilyl)phenyl triflate (**1a**) was allowed to react with **2a** in the presence of Na_2CO_3 in DME at 90 °C for 24 h (entry 6). When Cs_2CO_3, $NaHCO_3$, K_2CO_3 or Li_2CO_3 were used as the base, the yields ranged from 36% to 55% (entries 7–10). Surprisingly, the substitution of Na_2CO_3 by NaCl gave a 66% yield (entry 11). When the reaction was carried out in DME at 65 °C for 24 h, the conversion was only 15% (entry 12). When the amount of CsF was increased with or without the addition of a base in DME at 90 °C, only 29–64% yields of the desired product were obtained (entries 13–15). When the reactions were repeated in THF at 65 °C for 24 h, the yields were only 5% and 12% (entries 16 and 17). When the reaction was refluxed for 12 h, only a 36% yield of the desired product was obtained (entry 18). If additional (1.5 equiv) **1a** was used in the reaction, the desired product was still only formed in 61% and 48% yields (entries 19 and 20).

The cycloaddition of **1a** and **2a** was also examined using 2 equiv of tetrabutylammonium difluorotriphenylsilicate (TBAT) as the source of fluoride in DME for 24 h. The starting 2-*tert*-butyl-3-phenyl-1,2-oxaziridine was recovered at room temperature and none of the desired product was formed at 90 °C. Thus, CsF has been found to be a better source of fluoride for the formation of dihydrobenzisoxazoles.

Two different 'optimized' conditions, Method A [**1a** (0.3 mmol), 1.2 equiv of **2a**, 3 equiv of CsF and 1.1 equiv of Na_2CO_3 at 90 °C for 24 h] and Method B [**1a** (0.3 mmol), 1.2 equiv of **2a** and 4.5 equiv of CsF at 90 °C for 24 h] were chosen for the synthesis of additional dihydrobenzisoxazoles by this [3+2] cycloaddition process.

Synthesis of Dihydrobenzisoxazoles

Five different oxaziridines were allowed to react with *o*-(trimethylsilyl)phenyl triflate (**1a**) using our two optimized conditions, Methods A or B, to compare the yields of the desired products. Using Method A, a 77% yield of **3aa** was achieved, while only a 64% yield of **3aa** was obtained using Method B (Table 3, entry 1). Higher yields were also observed using Method A when oxaziridines **2b** or **2c** were allowed to react with the benzyne precursor **1a** (entries 2 and 3). However, **3aj** and **3ak**, containing cyclohexyl and isopropyl groups on the nitrogen of the oxaziridine respectively, produced less than 5% yields of the desired products using these methods (entries 4 and 5). These results may be related to the instability of the oxaziridines or the corresponding dihydrobenzisoxazoles at these reaction temperatures. Dihydrobenzisoxazoles have relatively weak N-O bonds, which may result in decomposition of the product at higher temperatures. In the light of these results, Method A would appear to be a better procedure for the synthesis of dihydrobenzisoxazoles. It appears that the thermal stability of the oxaziridine significantly affects the [3+2] cycloaddition reaction with arynes. As noted above, the more stable oxaziridines give the higher yields of the desired products.

The scope and limitations of this methodology for the formation of dihydrobenzisoxazoles using a wide range of oxaziridines, including aromatic, polycyclic, heterocyclic and aliphatic oxaziridines, were examined (Table 3). The reaction of oxaziridines bearing substituted aromatic rings usually afforded the corresponding products in moderately good yields (entries 2, 3, 6–8, 13–21, and 23–26). The *para*-substituted benzyloxy- and methoxy-aryl oxaziridines gave higher yields of cycloadduct than our model system (entries 6 and 7). However, when a strong electron-withdrawing nitro group was present on the aromatic ring (**2g**), the dihydrobenzisoxazole product was not observed even after 24 h (entry 8). While the highest yield (88%) was obtained from the reaction of **1a** and 2-*tert*-butyl-3-(fur-2-yl)-1,2-oxaziridine (entry 9), the electron-poor 3-pyridyl heterocyclic substrate **2f** gave a very low yield of the desired product (entry 10). The reaction of aliphatic-substituted oxaziridines, such as 2-*tert*-butyl-3-isopropyl-1,2-oxaziridine (**2i**), with **1a** was performed to investigate the effect of aliphatic groups on the formation of dihydrobenzisoxazoles. A very low yield was observed for **3ai** (entry 11) under our optimized conditions. When 2-(1-ethynylcyclohexyl)-3-phenyl-1,2-oxaziridine (**2o**) was used for the synthesis of **3ao**, only a 12% yield was obtained (entry 12). Dihydrobenzisoxazoles **3an**, **3aq**, **3ar, 3as** and **3ax** were synthesized in 40–53% isolated yields from the corresponding *ortho*-substituted aryl oxaziridines (entries 13–17). These relatively low yields are apparently caused by steric effects arising from the *ortho* positions of the aromatic rings. Analogous *m*-substituted aryl oxaziridines on the other hand afforded good yields of the corresponding dihydrobenzisoxazoles **3ap** and **3at** (entries 18 and 19). While benzyne precursor **1a** appeared to react with bicyclic oxaziridine **2l** to afford the corresponding polycyclic dihydrobenzisoxazole (entry 22), the desired polycyclic product **3al** could not be isolated cleanly from the reaction.

Additional examples of the reaction of oxaziridines **2e** and **2m** with a variety of aryne precursors (Figure 1) were conducted under our optimized conditions to obtain a variety of substituted dihydrobenzisoxazoles in moderate yields (entries 23–26). The electron-rich dimethyl-substituted benzyne gave lower yields (21%, entry 23; 56%, entry 24) than the analogous reactions of the parent benzyne. The electron-poor difluoroaryne analogue reacted

with 3-[4-(benzyloxy)phenyl]-2-*tert*-butyl-1,2-oxaziridine (**2m**) to form the corresponding product in a good yield (64%, entry 25). In addition, the unsymmetrical naphthalyne precursor **1d** reacted with 2-*tert*-butyl-3-(4-methoxyphenyl)-1,2-oxaziridine (**2e**) to produce **3de** in a 32% isolated yield as the only regioisomer (entry 26). This regioselectivity presumably arises from nucleophilic attack of the oxaziridine selectively at the C-2 position of the naphthalyne intermediate due to more favorable steric and electronic effects. In fact, similar regioselectivity has been observed in our previous studies with substituted arynes.[23,27] Suzuki *et al.* have also pointed out that the regiochemistry of [3+2] dipolar cycloaddition reactions depends on the C-3 substituent of the aryne.[1f] The reaction between arynes and oxaziridines generally gives a diastereomeric mixture of dihydrobenzisoxazoles due to the diastereomeric starting compound. However, the diastereomers have not been separated by column chromatography. The stereogenic carbon atom present in the diastereomers is evident as two peaks in the ^{13}C NMR spectrum.

Mechanism for Formation of the Dihydrobenzisoxazoles

Two reaction mechanisms are possible for the cycloaddition of oxaziridines and arynes (Scheme 1). In the first possible mechanism (Path A), insertion of the aryne into the C-O bond of the oxaziridine ring occurs by a concerted mechanism. Agawa[28] and Troisi[4] have suggested a similar cycloaddition mechanism for the formation of diarylisoxazolidine derivatives from oxaziridines. Another possible mechanism involves initial formation of a nitrone at the higher temperatures employed. We have recently observed that nitrones react readily with arynes to give dihydrobenzisoxazoles.[29] Troisi *et al*. have also compared the one-step mechanism to the nitrone mechanism in similar cyclization reactions.[3,4] They suggest that Path A is more probable than the nitrone mechanism. It is important to note that this is one of only a few known reactions of oxaziridines in which insertion occurs between the carbon and oxygen of the oxaziridine, rather than the oxygen and nitrogen.[30]

Recently, the synthesis of a wide variety of poly-substituted heterocyclics and polycyclics has been reported using various palladium-catalyzed cross-couplings, such as Sonogashira,[31] Suzuki-Miyaura,[32] and Heck[33] cross-couplings. We believe that our approach to halogen-substituted dihydrobenzisoxazoles could be very useful for the synthesis of additional, more highly substituted dihydrobenzisoxazoles. Thus, we have been able to convert **3at** and **3av** to the corresponding methoxypyridyl-substituted dihydrobenzisoxazoles using a modified Suzuki-Miyaura literature procedure (Scheme 2).[34] The halogen-substituted dihydrobenzisoxazoles **3at** and **3av** were allowed to react with the indicated boronic acids to form **4at** and **4av** in the presence of Cs_2CO_3 and 10 mol % of $Pd(PPh_3)_4$ under microwave irradiation for 20 min. Dihydrobenzisoxazoles **4at** and **4av** were obtained in 58% and 72% yields, respectively. By allowing compound **3av** to react with a terminal alkyne in the presence of 2 mol % of $PdCl_2(PPh_3)_2$ and 1 mol % CuI under microwave conditions for 20 min at 65 °C, the elaborated product **5av** was isolated in a 76% yield by Sonogashira coupling (Scheme 3). Thus, halogen-substituted dihydrobenzisoxazoles produced by the cycloaddition of oxaziridines and arynes can be easily elaborated to more highly substituted derivatives to afford potentially biologically active derivatives.

Conclusions

In the present study, a novel synthetic route to a variety of dihydrobenzisoxazoles by the [3+2] cycloaddition reaction of arynes and oxaziridines has been developed. The reaction tolerates a variety of oxaziridines and silylaryl triflates and affords the corresponding cycloadducts in moderate to good yields. This process is one of the few such reactions of oxaziridines, which is observed to proceed by carbon-oxygen bond cleavage of the oxaziridine. The resulting halogen-substituted dihydrobenzisoxazoles are readily elaborated

to more complex products using known organopalladium chemistry. This methodology provides a useful new route for the synthesis of substituted dihydrobenzisoxazoles, which should find application in the construction of molecules with interesting biological properties and pharmaceutical potential.

Experimental Section

General Procedure for the Synthesis of Dihydrobenzisoxazoles

To a mixture of CsF (0.90 mmol, 3 equiv) and Na_2CO_3 (0.33 mmol, 1.1 equiv) in a 4-dram vial was added a solution of the *o*-(trimethylsilyl)aryl triflate (0.30 mmol) and oxaziridine (0.36 mmol, 1.2 equiv) in 5 ml of DME. The resulting mixture was flushed with Ar and stirred at 90 °C for 24 h. After the reaction was over, the DME was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

2-*tert*-Butyl-3-phenyl-2,3-dihydrobenz[*d*]isoxazole (3aa)—Purification by flash chromatography (1:20 ethyl acetate/hexane) afforded the product as a white solid: mp 93.3–95.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (m, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.80 (m, 2H), 5.60 (s, 1H), 1.19 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.3, 144.1, 130.0, 128.8, 127.6, 127.5, 123.8, 120.9, 106.9, 67.2, 61.3, 25.7. HRMS (EI) calcd for $C_{17}H_{19}NO$: 253.1467, found 253.1471.

General Procedure for the Suzuki-Miyaura Coupling with Boronic Acids

To a solution of the dihydrobenzisoxazole (0.15 mmol) and boronic acid (0.18 mmol) in a microwave vial in 1:1 DMF/EtOH (2 ml) were added $Pd(PPh_3)_4$ (0.015 mmol) and Cs_2CO_3 (0.20 mmol). The resulting vial was sealed and stirred under microwave irradiation at the appropriate temperature for 20 min. The resulting solution was diluted with satd aq NH_4Cl (15 mL) and extracted with dichloromethane (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

2-*tert*-Butyl-3-[3-(5-methoxypyridin-2-yl)phenyl]-2,3-dihydrobenz[*d*]isoxazole (4at)—The reaction was carried out at 120 °C. Purification by flash chromatography (1:20 ethyl acetate/hexane) afforded the product as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.58 (s, 1H), 7.42 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.82 (m, 3H), 5.67 (s, 1H), 3.98 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8, 156.4, 145.3, 144.9, 138.4, 137.7, 132.2, 130.1, 129.7, 129.4, 128.9, 126.5, 125.9, 123.8, 120.9, 110.9, 107.0, 67.0, 61.3, 53.8, 25.7. HRMS (EI) calcd for $C_{23}H_{24}N_2O_2$: 360.1838, found 360.1848.

General Procedure for Sonogashira Coupling with a Terminal Alkyne

To a solution of the dihydrobenzisoxazole (0.15 mmol) and terminal alkyne (0.18 mmol) in a microwave vial in 1:1 DMF/Et_3N (2 ml) were added $PdCl_2(PPh_3)_2$ (0.003 mmol) and CuI (0.0015 mmol). The resulting vial was sealed and stirred under microwave irradiation at 65 °C for 20 min. The resulting solution was diluted with satd aq NH_4Cl (15 mL) and extracted with dichloromethane (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

2-*tert*-Butyl-3-[3,4-dimethoxy-5-(2-(3,5-dimethoxyphenyl)ethynyl)phenyl]-2,3-dihydro- benz[*d*]isoxazole (5av)—Purification by flash chromatography (1:20 ethyl

acetate/hexane) afforded the product as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.82 (m, 2H), 6.71 (s, 2H), 6.47 (s, 1H), 5.55 (s, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H), 1.20 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.7, 156.1, 153.1, 149.8, 139.9, 129.5, 128.9, 124.8, 123.8, 123.4, 120.9, 117.5, 112.2, 109.5, 107.0, 102.0, 93.6, 85.4, 66.8, 61.2, 56.3, 55.6, 25.7. HRMS (EI) calcd for $C_{29}H_{31}NO_5$: 473.2202, found 473.2215.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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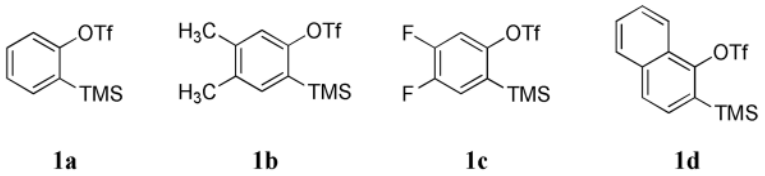
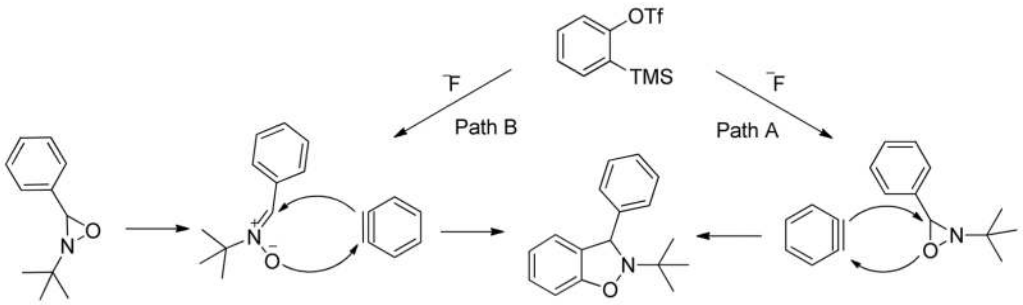
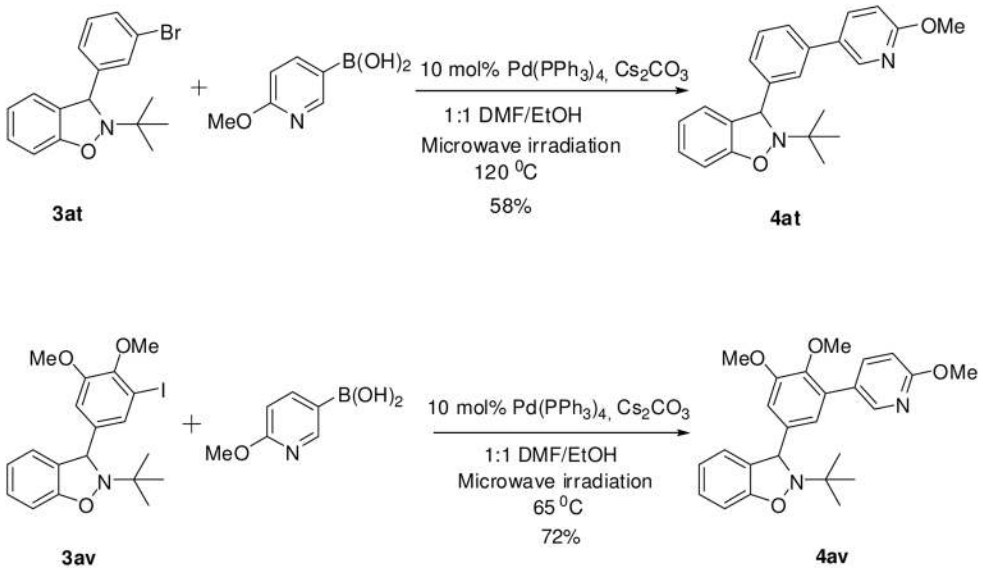


1a **1b** **1c** **1d**

FIGURE 1.
Aryne precursors.

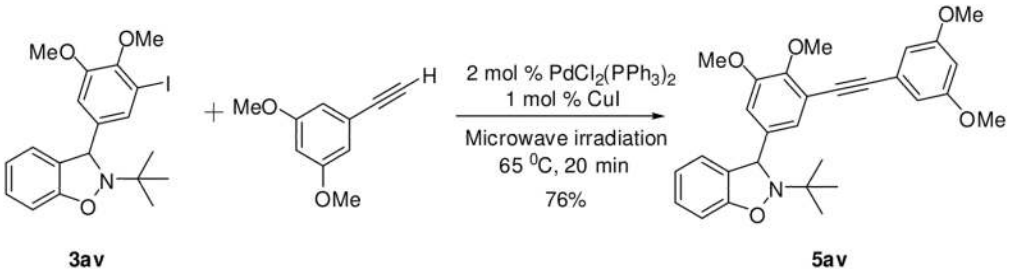


SCHEME 1.
Possible Mechanisms for Formation of the Dihydrobenzisoxazoles



SCHEME 2.

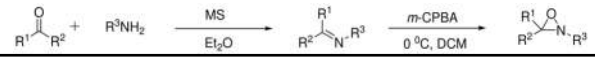
The Suzuki-Miyaura Coupling of Dihydrobenzisoxazoles with Boronic Acids

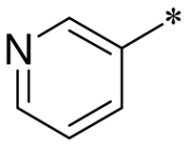
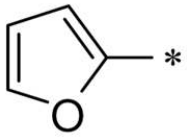
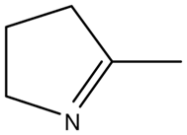
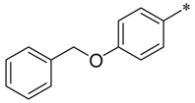


SCHEME 3.
The Sonogashira Coupling of a Dihydrobenzisoxazole and a Terminal Alkyne

TABLE 1

Synthesis of Oxaziridines



entry	R^1	R^2	R^3	oxaziridine	% yield[a]
1	Ph	H	*t*-butyl	**2a**	65
2	*o*-BrC_6H_4	H	*t*-butyl	**2b**	67
3	2-naphthyl	H	*t*-butyl	**2c**	40
4	Ph	H	*n*-butyl	**2d**	43
5	*p*-$MeOC_6H_4$	H	*t*-butyl	**2e**	44
6		H	*t*-butyl	**2f**	65
7	*p*-$O_2NC_6H_4$	H	*t*-butyl	**2g**	66
8		H	*t*-butyl	**2h**	15
9	isopropyl	H	*t*-butyl	**2i**	37
10	Ph	H	cyclohexyl	**2j**	53
11	Ph	H	isopropyl	**2k**	40
12		-	-	**2l**	55
13		H	*t*-butyl	**2m**	62

J Org Chem. Author manuscript; available in PMC 2011 November 5.

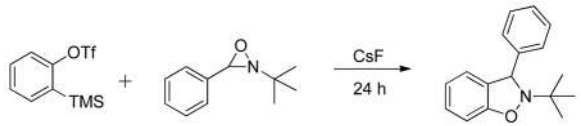
entry	R^1	R^2	R^3	oxaziridine	% yield[a]
14		H	*t*-butyl	**2n**	35
15	Ph	H		**2o**	56
16	*m*-$MeOC_6H_4$	H	*t*-butyl	**2p**	63
17		H	*t*-butyl	**2q**	67
18		H	*t*-butyl	**2r**	59
19		H	*t*-butyl	**2s**	63
20	*m*-BrC_6H_4	H	*t*-butyl	**2t**	67
21		H	*t*-butyl	**2u**	49

entry	R^1	R^2	R^3	oxaziridine	% yield[a]
22		H	*t*-butyl	**2v**	55
23		H	*t*-butyl	**2x**	70

[a]The overall yield from the carbonyl starting material.

TABLE 2

Optimization of the Reaction of Oxaziridine 2a and Benzyne Precursor 1a.



1a **2a** **3aa**

entry	CsF (equiv)	base (equiv)	solvent	temp (°C)	% 3aa	% 2a
1	3	-	CH_3CN	RT	-	>98
2	3	-	CH_3CN	65	trace	66
3	3	-	DME	90	59	-
4	3	-	Toluene	110	13	-
5	3	-	DMF	110	-	-
6[a]	**3**	**Na_2CO_3 (1.1)**	**DME**	**90**	**77**	**-**
7[b]	3	Cs_2CO_3 (1.1)	DME	90	36	8
8	3	$NaHCO_3$ (1.1)	DME	90	42	-
9[b]	3	K_2CO_3 (1.1)	DME	90	45	7
10[b]	3	Li_2CO_3 (1.1)	DME	90	55	25
11	3	NaCl (1.1)	DME	90	66	-
12[b]	3	Na_2CO_3 (1.1)	DME	65	15	85
13[c]	**4.5**	**-**	**DME**	**90**	**64**	**-**
14	6	-	DME	90	46	-
15	4.5	Na_2CO_3 (1.1)	DME	90	29	-
16	3	Na_2CO_3 (1.1)	THF	65	12	88
17[b]	4.5	-	THF	65	5	5
18[d]	3	Na_2CO_3 (1.1)	DME	90	36	63
19 [e]	3	Na_2CO_3 (1.1)	DME	90	61	-
20[e]	4.5	-	DME	90	48	-

[a]Method A: the reaction was carried out on **1a** (0.3 mmol), 1.2 equiv of **2a**, 1.1 equiv of Na_2CO_3 and 3 equiv of CsF in DME (7 ml) at 90 °C for 24 h.

[b] Yields were determined by proton NMR spectral analysis.

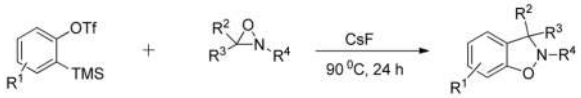
[c] Method B: the reaction was carried out on **1a** (0.3 mmol), 1.2 equiv of **2a**, 4.5 equiv of CsF in DME (7 ml) at 90 °C for 24 h.

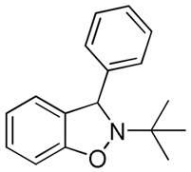
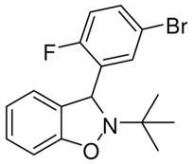
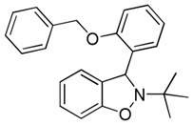
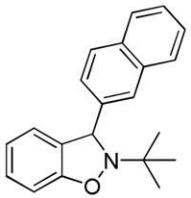
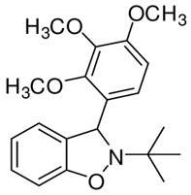
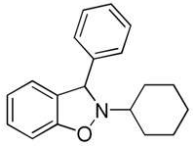
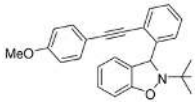
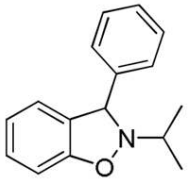
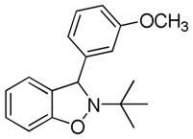
[d] The yield was calculated from the crude product and the reaction time was 12 h.

[e] 1.5 Equiv of *o*-(trimethylsilyl)phenyl triflate (**1a**) was used for these cyclization reactions.

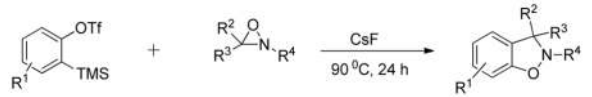
TABLE 3

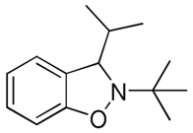
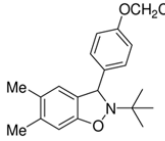
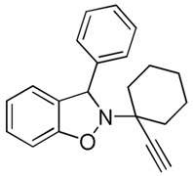
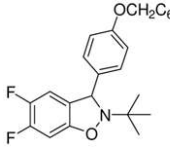
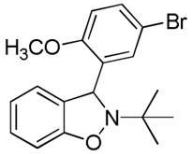
Synthesis of Substituted Dihydrobenzisoxazoles from Arynes and Oxaziridines



entry	product		method	% yield	entry	product		method	% yield
1		**3aa**	A B	77 64	14[a]		**3aq**	A	42
2		**3ab**	A B	59 43	15		**3ar**	A	50
3		**3ac**	A B	71 58	16		**3as**	A	50
4		**3aj**	A B	<5 <5	17		**3ax**	A	53
5		**3ak**	A B	<5 <5	18		**3ap**	A	77

entry	product		method	% yield	entry	product		method	% yield
6		**3ae**	A	78	19		**3at**	A	70
7		**3am**	A	86	20		**3au**	A	79
8		**3ag**	A	<5	21		**3av**	A	66
9		**3ah**	A	88	22		**3al**	A	0
10		**3af**	A	<5	23[b]		**3be**	A	21



entry	product		method	% yield	entry	product		method	% yield
11		**3ai**	A	<5	24[b]		**3bm**	A	56
12[a]		**3ao**	A	12	25[c]		**3cm**	A	64
13		**3an**	A	40	26[d]		**3de**	A	32

[a]The yield was calculated from integration of the ^{1}H NMR spectrum.

[b]4,5-Dimethyl-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

[c]4,5-Difluoro-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

[d]2-(Trimethylsilyl)naphthlen-1-yl triflate was used as the aryne precursor.

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