Convenient Approach to 3,4-Diarylisoxazoles Based on the Suzuki Cross-Coupling Reaction

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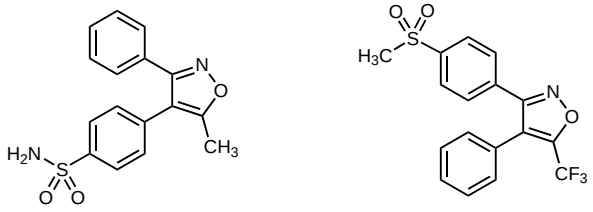
Abstract: The Suzuki cross-coupling reaction was found effective for rapid access to a series of 3,4-diarylisoxazoles of pharmacological interest. The efficiency of this approach was demonstrated by the synthesis of the highly potent COX-2-selective inhibitor, 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib), and its analogues. Thus, the coupling reaction between (3-aryl-5-methyl-4-isoxazolyl)boronic acids, prepared *in situ* from the corresponding bromides using triisopropyl borate, and aryl bromides containing a 4-sulfonamide or 4-methylsulfonyl group under the standard conditions [$Pd(PPh_3)_4$, Na_2CO_3, EtOH-H_2O, reflux] yielded the target 3,4-diarylisoxazoles in good yields.

Keywords: COX-2 inhibitors; cross-coupling; 3,4-diarylisoxazoles; heterocycles; Suzuki reaction

Introduction

A 3,4-diarylisoxazole scaffold has frequently been incorporated into the pharmacophore design for a wide range of pharmaceutical agents. Some examples include non-steroidal anti-inflammatory drugs (NSAIDs),[1] proteins kinase inhibitors,[2] hypertensive agents[3] and estrogen receptor modulators.[4] The discovery of cyclooxygenase-2 (COX-2) in the beginning of the last decade has set off a race to develop selective COX-2 inhibitors.[5] Selective COX-2 inhibitors are potential anti-inflammatory drugs with reduced side effects as compared to NSAIDs which are non-selective COX-1/COX-2 inhibitors.[6] From the evaluation of numerous compounds, diarylheterocycles and diarylcarbocycles with a 4-sulfonamide or 4-methylsulfonyl group in one of the phenyl rings have been identified as the pharmacophore for selective COX-2 inhibition.[5] Recently, several diarylheterocycles comprised of the 3,4-diarylisoxazole ring have shown extremely high COX-2 selectivity and potency, represented by 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib)[7] (**1**) and 3-(4-methylsulfonylphenyl)-4-phenyl-5-trifluoromethylisoxazole[8] (**2**) (Figure 1).

Although several methods are available for the synthesis of substituted isoxazoles,[9] selective methods to 3,4-diarylisoxazoles are limited and depend on the availability of proper starting compounds containing two aryl groups on adjacent carbons.[10] Krogsgaard-Larsen et al.[11] have recently reported the synthesis of 4-aryl-3-isoxazolols by palladium-catalyzed cross-coupling reactions between *O*-protected 4-iodo-3-isoxazolols and arylboronic acids. We have therefore investigated the feasibility of the Suzuki cross-coupling reaction[12] for the direct arylation of the 4-position of 3-arylisoxazoles, thus forming 3,4-diarylisoxazoles particularly **1** and its analogues. Such an approach is of particular interest in light of its amenability to synthesize 3,4-diarylisoxazoles by combinatorial methods.[13]



Valdecoxib (**1**) **2**

Figure 1. Highly potent COX-2-selective inhibitors comprised of a 3,4-diarylisoxazole scaffold.

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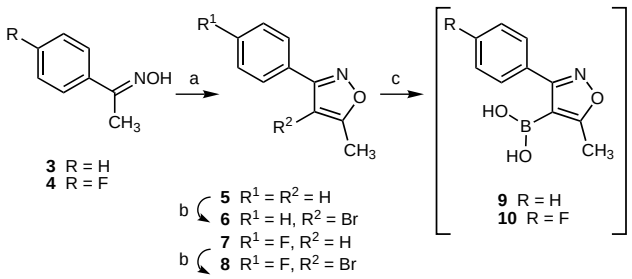
Results and Discussion

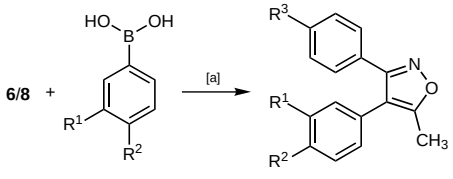
The 3-aryl-5-methylisoxazole **5**[14]/**7** was prepared from the known oxime **3**[15]/**4**[15] according to the standard procedure,[9] which involved generation of the 1,4-dilithium salt and subsequent condensation with EtOAc followed by dehydration (Scheme 1). Electrophilic bromination of **5**/**7** occurred predominantly at the 4-position of the isoxazole ring[16] affording **6**[17]/**8**. A sequence of metallation and treatment with triisopropyl borate transformed **6**/**8** into the boronic acid **9**/**10**.

The Suzuki cross-coupling reaction was first investigated using **6**/**8** and commercially available arylboronic acid **11**/**12** in aqueous EtOH using Na_2CO_3 as base and $Pd(PPh_3)_4$ (~3 mol %) as catalyst (Table 1). The reaction proceeded efficiently leading to the formation of the desired 3,4-diarylisoxazole **14**/**15** in good yield. However, the attempt to prepare the valdecoxib analogue **16** by the coupling reaction of **6** and the arylboronic acid **13**[18] was unsatisfactory; the expected coupling reaction was preceded by competitive protodeboronation. The two electron-withdrawing groups on **13** might facilitate base-catalyzed deboronation.[19] Interestingly, the 4,4′-dimethoxytrityl (DMT) group, used for the sulfonamide protection, was lost during the cross-coupling reaction.



Scheme 1. Conditions: (a) (1) BuLi (~2 equiv.), THF, −40 °C, 30 min, (2) EtOAc, −40 °C → rt, 2 h, (3) H_2SO_4, 80 °C, 2 h (**5**: 46%; **7**: 42%); (b) Br_2, CCl_4, 0 °C → rt, 2 h (**6**: 80%; **8**: 70%); (c) (1) BuLi, THF, −78 °C, 30 min, (2) $(i\text{-PrO})_3B$, −78 °C → rt, 2h.

Table 1. Suzuki cross-coupling reaction of 4-bromoisoxazoles and arylboronic acids.

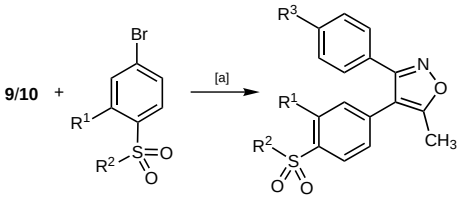


4-Bromo-isoxazole	R^1	R^2	R^3	Arylboronic acid	Product	Yield [%][b]
6	H	F	H	**11**	**14**	60
8	H	H	F	**12**	**15**	65
6	F	SO_2NHX	H	**13** (X = DMT[c])	**16** (X = H)	10[d]

[a] $Pd(PPh_3)_4$ (~3 mol %), Na_2CO_3, EtOH-H_2O, reflux, 12 h.
[b] Isolated yields based on 4-bromoisoxazoles and not optimized.
[c] DMT = 4,4′-dimethoxytrityl.
[d] 2-Fluorobenzenesulfonamide was isolated as the major product.

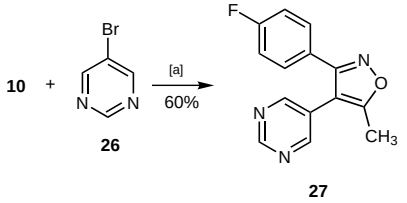
The coupling reaction was next investigated with the (3-aryl-4-isoxazolyl)boronic acid **9**/**10** and aryl bromides containing a 4-sulfonamide or 4-methylsulfonyl group[20] under identical conditions as above (Table 2). In this way valdecoxib (**1**) as well as its known analogues **22**[7a] and **23**[7a] and new analogues **16**, **24** and **25** were synthesized in good yields simply by variation of coupling partners. In contrast to the arylboronic acid **13**, the two electron-withdrawing groups on the aryl bromide **18** affected favorably the cross-coupling reaction (i.e., the syntheses of **16** and **24**).[21] The poor yield of **21** might be ascribed to the possibility that the vicinal nitro and sulfonamide groups on the aryl bromide **19** were acting as a bidentate chelating ligand for Pd, thus interfering with the catalytic cycle.[22] The direct heteroarylation of **10** with commercially available 5-bromopyrimidine (**26**) was also successful affording **27** in good yield (Scheme 2).

Table 2. Suzuki cross-coupling reaction of (4-isoxazolyl)-boronic acids and aryl bromides.



4-Isoxazolyl-boronic acid	R^1	R^2	R^3	Aryl bromide	Product	Yield [%][b]
9	H	NH_2	H	**17**	**1**	70
9	F	NH_2	H	**18**	**16**	75
9	NO_2	NH_2	H	**19**	**21**	30
9	H	CH_3	H	**20**	**22**	50
10	H	NH_2	F	**17**	**23**	60
10	F	NH_2	F	**18**	**24**	55
10	H	CH_3	F	**20**	**25**	50

[a] $Pd(PPh_3)_4$ (~3 mol %), Na_2CO_3, EtOH-H_2O, reflux, 12 h.
[b] Isolated yields based on aryl bromides and not optimized.



Scheme 2. Conditions: (a) $Pd(PPh_3)_4$ (~3 mol %), Na_2CO_3, EtOH-H_2O, reflux, 12 h.

Conclusions

The Suzuki cross-coupling reaction has proven effective for the synthesis of 3,4-diarylisoxazoles. This approach could allow for the rapid construction of a library of functionalized 3,4-diarylisoxazoles. Investigations along this line, further optimization of the coupling conditions and pharmacological evaluation of new valdecoxib analogues are currently in progress.

Experimental Section

General

THF and CH_2Cl_2 were distilled from sodium benzophenone ketyl and CaH_2, respectively, under a positive pressure of dry argon. The Suzuki cross-coupling reaction and the reactions below 0 °C were carried out under an argon atmosphere. ^1H and $^{19}F\{^1H\}$ NMR spectra were recorded on a Bruker AM360 in $CDCl_3$ or CD_3OD with TMS (for ^1H) and $CFCl_3$ (for ^{19}F) as internal standards. LRMS and HRMS were obtained on a VG ZAB-SE (for FABMS) and a VG 70VSE (Autospec) (for EIMS). Flash column chromatography was performed on ICN silica gel 60 (0.032 - 0.063 mm). The purity (>98%) of the products was checked by their ^1H NMR spectra.[23]

Representative Procedure for the Synthesis of 3-Aryl-5-methylisoxazoles 5 and 7: 3-(4-Fluorophenyl)-5-methylisoxazole (7)

A solution of 4′-fluoroacetophenone oxime[15] (**4**) (3.16 g, 20.7 mmol) in THF (20 mL) was treated with a 2.5 M solution of BuLi in hexanes (17.6 mL, 44.0 mmol) at −40 °C for 30 min. A solution of EtOAc (4.0 mL, 40.9 mmol) in THF (6 mL) was then added dropwise over a period of 20 min. The resulting mixture was allowed to warm to room temperature for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (4:1, v/v) afforded *3-(4-fluorophenyl)-5-hydroxy-5-methyl-2-isoxazoline* as a colorless solid; yield: 2.50 g (63%). ^1H NMR ($CDCl_3$): δ = 1.77 (s, 3H), 3.22 and 3.33 (AB q, 2H, J = 17 Hz), 7.07 (br t, 2H, J = 8.5 Hz), 7.62 (br dd, 2H, J = 8.5, 5.5 Hz). The product was used in the next step without further characterization.

A mixture of the product thus obtained (2.0 g, 10.4 mmol) and concentrated H_2SO_4 (30 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was poured slowly into crushed ice and the product was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (9:1, v/v) gave **7** as a colorless solid; yield 1.23 g (67%; 42% overall yield). ^1H NMR ($CDCl_3$): δ = 2.48 (s, 3H), 6.26 (s, 1H), 7.13 (br t, 2H, J = 8.5 Hz), 7.77 (br dd, 2H, J = 8.5, 5.5 Hz); ^{19}F NMR ($CDCl_3$): δ 75.81 (s); HREIMS: calcd. for $C_{10}H_8FNO$: 177.0590; found: 177.0587.

5-Methyl-3-phenylisoxazole[14] (**5**) was similarly synthesized from acetophenone oxime[15] (**3**) (2.7 g, 20.0 mmol) in 46% overall yield. The intermediate 5-hydroxy-5-methyl-3-phenyl-2-isoxazoline was characterized by ^1H NMR and HREIMS: ^1H NMR ($CDCl_3$): δ = 1.78 (s, 3H), 3.24 and 3.37 (AB q, 2H, J = 17 Hz), 3.63 (br s, 1H), 7.35–7.45 (m, 3H), 7.60–7.65 (m, 2H); HREIMS: calcd. for $C_{10}H_{11}NO_2$: 177.0790; found: 177.0790.

Representative Procedure for the Bromination of 5 and 7: 4-Bromo-3-(4-fluorophenyl)-5-methylisoxazole (8)

A 10% (v/v) solution of Br_2 in CCl_4 (40 mL) was added dropwise to a solution of **7** (885 mg, 5.0 mmol) in CCl_4 (15 mL) at 0 °C over a period of 1 h. The mixture was allowed to warm to room temperature for 2 h. The mixture was then diluted with 10% (wt/wt) aqueous NaOH and the product was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (95:5, v/v) afforded **8** as a colorless solid; yield: 900 mg (70%). ^1H NMR ($CDCl_3$): δ = 2.50 (s, 3H), 7.18 (br t, 2H, J = 8.5 Hz), 7.80–7.90 (br dd, 2H, J = 8.5, 5.5 Hz); ^{19}F NMR ($CDCl_3$): δ = 76.56 (s); HREIMS: calcd. for $C_{10}H_8BrFNO$: 255.9787; found: 255.9773.

4-Bromo-5-methyl-3-phenylisoxazole[17] (**6**) was similarly synthesized from **5** (2.0 g, 12.6 mmol) in 80% yield.

Preparation of Arylboronic Acids 9 and 10

A solution of the corresponding bromide (i.e., **6** and **8**) (1 mmol) in THF (5 mL) was treated with a 2.5 M solution of BuLi in hexanes (1.2 equiv.) at −78 °C for 30 min. A solution of triisopropyl borate (2 mL, 8.6 equiv.) in THF (5 mL) was then added dropwise over a period of 20 min. The resulting mixture was allowed to warm to room temperature over a period of 2 h. The reaction was quenched by addition of brine and the product was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was used directly in the Suzuki cross-coupling reaction without further purification and characterization.

Preparation of the Arylboronic Acid 13

A solution of 4,4′-dimethoxytrityl chloride (1.1 g, 3.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of 4-bromo-2-fluorobenzenesulfonamide[20] (**18**) (760 mg, 3.0 mmol) and Et_3N (0.7 mL, 5.5 mmol) in CH_2Cl_2-THF (20 mL, 1:1, v/v) with stirring at 0 °C. The resulting mixture was allowed to warm to room temperature for 1 h. The reaction mixture was then concentrated to dryness. Flash column chromatography with hexanes-EtOAc (4:1, v/v) afforded *4-bromo*-N-*(4,4′-dimethoxytrityl)-2-fluorobenzenesulfonamide* as a pale yellow solid; yield: 1.67 g (95%). ^1H NMR ($CDCl_3$): δ = 3.75 (s, 6H), 5.91 (br s, 1H), 6.65 (br d, 4H, J = 8.5 Hz), 6.74 (t, 1H, J = 8.0 Hz), 6.97 (br d, 1H, J = 8.5 Hz), 7.10–7.35 (m, 8H), 7.42 (br d, 2H, J = 7.5 Hz); ^{19}F NMR: δ = 77.39 (s); HREIMS: calcd. for $C_{27}H_{23}BrFNO_4S$: 555.0515; found: 555.0513.

A solution of the bromide thus obtained (230 mg, 0.4 mmol) in THF (10 mL) was treated with a 2.5 M solution of BuLi in hexanes (0.44 mL, 1.1 mmol) at $-78\,^{\circ}C$ for 30 min. A solution of triisopropyl borate (1.0 mL, 4.3 mmol) in THF (5 mL) was then added dropwise and the mixture was allowed to warm to room temperature over a period of 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and the product was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was subjected to flash column chromatography using two sequential eluants, i.e., hexanes-EtOAc (4:1, v/v) and then hexanes-EtOAc (2:3, v/v).

The first eluant furnished N-*(4,4′-dimethoxytrityl)-2-fluorobenzenesulfonamide* as a pale yellow solid; yield: 100 mg (51%). ^{1}H NMR ($CDCl_3$): $\delta = 3.73$ (s, 6H), 5.92 (br s, 1H), 6.64 (br d, 4H, $J = 9$ Hz), 6.83 (br t, 1H, $J = 7.5$ Hz), 6,88 (br t, 1H, $J = 7.5$ Hz), 6.96 (br d, 1H, $J = 7.5$ Hz), 7.15 – 7.35 (m, 8H), 7.42 (br d, 2H, $J = 7$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = 74.98$ (s); LREIMS: $m/z = 477$ (M^+), 303 (4,4′-dimethoxytrityl).

The second eluant gave **13** as a pale yellow solid; yield: 120 mg (56%). ^{19}F NMR ($CDCl_3$): $\delta = 76.13$ (s); LREIMS: $m/z = 303$ (4,4′-dimethoxytrityl). This product was used in the Suzuki cross-coupling reaction without further characterization.

Representative Procedure for the Suzuki Cross-Coupling Reaction of 4-Bromoisoxazoles and Arylboronic Acids: 3-(4-Fluorophenyl)-5-methyl-4-phenylisoxazole (15)

A mixture of **8** (90 mg, 0.35 mmol), phenylboronic acid **12** (60 mg, 0.50 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), EtOH (6 mL) and 2 M aqueous Na_2CO_3 (1 mL) was refluxed for 12 h. After cooling to room temperature, the mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (7:3, v/v) afforded **15** as a colorless solid; yield: 58 mg (65% based on **8**). ^{1}H NMR (CD_3OD): $\delta = 2.39$ (s, 3H), 7.03 (br t, 2H, $J = 8.5$ Hz), 7.15 (br dd, 2H, $J = 7.5$, 1.5 Hz), 7.30 – 7.40 (m, 5H); ^{19}F NMR (CD_3OD): $\delta = 77.21$ (s); HREIMS: calcd. for $C_{16}H_{12}FNO$: 253.0903; found: 253.0904.

4-(4-Fluorophenyl)-5-methyl-3-phenylisoxazole (**14**) was similarly synthesized from **6** (90 mg, 0.38 mmol) and 4-fluorophenylboronic acid (**11**) (80 mg, 0.57 mmol) using $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) as a colorless solid; yield: 60% based on **6**.^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s. 3H), 6.97 (br t, 2H, $J = 8.5$ Hz), 7.00 – 7.10 (m, 2H), 7.20 – 7.35 (m, 5H); ^{19}F NMR ($CDCl_3$): $\delta = 72.71$ (s); HREIMS: calcd. for $C_{16}H_{12}FNO$: 253.0903; found: 253.0907.

Attempt to Synthesize 2-Fluoro-4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (16) by the Suzuki Cross-Coupling Reaction of 6 and 13

A mixture of **6** (52 mg, 0.22 mmol), **13** [190 mg, prepared using 0.6 mmol of 4-bromo-*N*-(4,4′-dimethoxytrityl)-2-fluorobenzenesulfonamide as described above], $Pd(PPh_3)_4$ (10 mg, 0.0086 mmol), EtOH (6 mL) and 2 M aqueous Na_2CO_3 (1 mL) was refluxed for 12 h. After cooling to room temperature, the mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (7:3, v/v) gave two fractions.

The first fraction yielded *2-fluorobenzensulfonamide* as a white powder; yield: 33 mg. ^{1}H NMR (CD_3OD): $\delta = 7.29$ (br q, 2H, $J = 8$ Hz), 7.61 (br q, 1H, $J = 10$ Hz), 7.86 (br t, 1H, $J = 7.5$ Hz); ^{19}F NMR (CD_3OD): $\delta = 77.86$ (s); HREIMS: calcd. for $C_6H_6FNO_2S$: 175.0103; found: 175.0108.

The second fraction afforded **16** as a colorless solid; yield: 7 mg (10% based on **6**). The successful synthesis of **16** and its physical data are given below.

Representative Procedure for the Suzuki Cross-Coupling Reaction of 4-Isoxazolylboronic Acids and Aryl/Heteroaryl Bromides: 2-Fluoro-4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (16)

A mixture of **9** (prepared using 1 mmol of **6** as described above), 4-bromo-2-fluorobenzenesulfonamide[20] (**18**) (150 mg, 0.59 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), EtOH (6 mL) and 2 M aqueous Na_2CO_3 (1 mL) was refluxed for 12 h. After cooling to room temperature, the mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness. Flash column chromatography with hexanes-EtOAc (3:2, v/v) afforded **16** as a colorless solid; yield: 147 mg (75% based on **18**). ^{1}H NMR (CD_3OD): $\delta = 2.47$ (s, 3H), 7.07 – 7.15 (m, 2H), 7.30 – 7.45 (m, 5H), 7.83 (br t, 1H, $J = 7.5$ Hz); ^{19}F NMR (CD_3OD): $\delta = 78.69$ (s); HREIMS: calcd. for $C_{16}H_{13}FN_2O_3S$: 332.0630; found: 332.0623.

4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (Valdecoxib)[7] (**1**) was similarly synthesized from **9** (prepared from 1 mmol of **6**) and 4-bromobenzenesulfonamide[20] (**17**) (140 mg, 0.59 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 70% based on **17**.

4-(5-Methyl-3-phenyl-4-isoxazolyl)-2-nitrobenzenesulfonamide (**21**) was similarly synthesized from **9** (prepared from 1 mmol of **6**) and 4-bromo-2-nitrobenzenesulfonamide (**19**) (165 mg, 0.59 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 30% based on **19**. ^{1}H NMR (CD_3OD): $\delta = 2.49$ (s, 3H), 7.30 – 7.50 (m, 5H), 7.56 (dd, 1H, $J = 8.5$, 1.8 Hz), 7.67 (d, 1H, $J = 1.8$ Hz), 8.06 (d, 1H, $J = 8.5$ Hz); HREIMS: calcd. for $C_{16}H_{13}N_3O_5S$: 359.0576; found: 359.0572.

5-Methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole[7a] (**22**) was similarly synthesized from **9** (prepared from 1 mmol of **6**) and 1-bromo-4-(methylsulfonyl)benzene (**20**) (140 mg, 0.60 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 50% based on **20**.

4-[3-(4-Fluorophenyl)-5-methyl-4-isoxazolyl]benzenesulfonamide[7a] (**23**) was similarly synthesized from **10** (prepared from 1 mmol of **8**) and **17** (140 mg, 0.59 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 60% based on **17**.

2-Fluoro-4-[3-(4-fluorophenyl)-5-methyl-4-isoxazolyl]benzenesulfonamide (**24**) was similarly synthesized from **10** (prepared from 1 mmol of **8**) and **18** (150 mg, 0.59 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 55% based on **18**. ^{1}H NMR ($CDCl_3$): $\delta = 2.43$ (s, 3H), 5.05 (br s, 2H), 6.90 – 7.05 (m, 4H), 7.31 (br dd, 2H, $J = 8.5$, 5.5 Hz), 7.86

(t, 1H, $J = 8.0$ Hz); ^{19}F NMR ($CDCl_3$): $\delta = 76.20$ (s), 76.42 (s); HREIMS: calcd. for $C_{16}H_{12}F_2N_2O_3S$: 350.0537; found: 350.0541.

3-(4-Fluorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]-isoxazole (**25**) was similarly synthesized from **10** (prepared from 1 mmol of **8**) and **20** (140 mg, 0.60 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 50% based on **20**. ^{1}H NMR (CD_3OD): $\delta = 2.49$ (s, 3H), 3.14 (s, 3H), 7.12 (br t, 2H, $J = 8.5$ Hz), 7.40 (br dd, 2H, $J = 8.5$, 5.5 Hz), 7.46 (br d, 2H, $J = 8$ Hz), 7.97 (br d, 2H, $J = 8$ Hz); ^{19}F NMR (CD_3OD): $\delta =$ 75.92; HREIMS: calcd. for $C_{17}H_{14}FNO_3S$: 331.0678; found: 331.0671.

3-(4-Fluorophenyl)-5-methyl-4-(5-pyrimidinyl)isoxazole (**27**) was similarly synthesized from **10** (prepared from 1 mmol of **8**) and 5-bromopyrimidine (**26**) (95 mg, 0.60 mmol) using $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) as a colorless solid; yield: 60% based on **26**. ^{1}H NMR ($CDCl_3$): $\delta = 2.46$ (s, 3H), 7.01 (br t, 2H, $J = 8.5$ Hz), 7.30 (br dd, 2H, $J = 8.5$, 5.5 Hz), 8.51 (s, 2H), 9.15 (s, 1H); ^{19}F NMR ($CDCl_3$): $\delta = 76.38$; HREIMS: calcd. for $C_{114}H_{10}FN_3O$: 255.0808; found: 255.0805.

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