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Synthesis of Aryl- and Heteroaryl-Substituted 3-Benzyloxyisothiazoles via Suzuki and Negishi Cross-Coupling Reactions

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Received October 27, 2003

Abstract: Introduction of aryl and heteroaryl substituents into the 5-position of 3-benzyloxyisothiazole (**1**) using palladium-catalyzed Suzuki and Negishi cross-coupling reactions was investigated. Attempts to generate synthetically viable nucleophilic species from **1** for Suzuki- or Negishi-type cross-couplings were unsuccessful. However, using 3-benzyloxy-5-iodoisothiazole **2** as an intermediate, a range of aromatic and heteroaromatic substituents were successfully introduced under Suzuki or Negishi cross-coupling conditions in good to excellent yields.

Bioisosteric substitution of acidic 5- or 6-membered heteroaromatic acidic units for carboxyl groups has been successfully used in many areas of drug design. One such example is 3-hydroxyisoxazole, which has been extensively used in the design of subtype-selective ligands for 4-aminobutanoic acid (GABA)[1] as well as (*S*)-glutamate (Glu)[2] receptors in the central nervous system. Thus, the 3-hydroxyisoxazole analogue of GABA, muscimol (Figure 1), a constituent of the mushroom *Amanita muscaria* interacting nonselectively with the $GABA_A$-subtype of GABA receptors,[3,4] has been effectively used as a lead structure for the design of a number of specific $GABA_A$ receptor ligands, including 4,5,6,7-tetrahydroisoxazolo-[5,4-*c*]pyridin-3-ol (THIP).[3] THIP is currently studied clinically as a potential drug for the treatment of pain and insomnia.[1]

The 3-hydroxyisoxazole analogue of Glu, [(*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propanoic acid, AMPA] (Figure 1), is a potent and highly selective agonist, acting specifically at the AMPA subtype of glutamate receptors.[2] Replacement of the 5-methyl substituent of AMPA by a range of aromatic and, in particular, heteroaromatic substituents has provided a range of interesting Glu receptor ligands,[5−7] including the 2-furyl-substituted analogue, 2-Fu-AMPA (Figure 1), which is markedly more potent than AMPA as an AMPA receptor agonist.[7]

Compared to 3-hydroxyisoxazole, 3-hydroxyisothiazole has been much less investigated as a carboxyl group bioisosteric unit. The isothiazole analogues of muscimol and AMPA, thiomuscimol and thio-AMPA, respectively, are examples of isothiazole-based compounds active at GABA and Glu receptors.[4,8] Although the 3-hydroxyisothiazole unit is less acidic than the 3-hydroxyisoxazole unit, thio-AMPA and thiomuscimol exhibit pharmacological characteristics very similar to those of AMPA and muscimol, respectively.[8,9] Interestingly, however, the 5-*tert*-butyl analogues of AMPA and thio-AMPA activate subtypes of Glu receptors differently.[10,11]

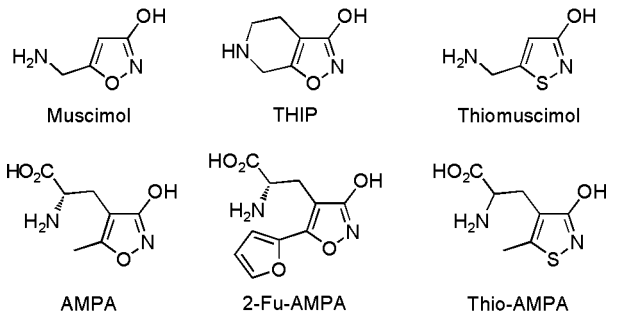

FIGURE 1. Structures of some isoxazole- and isothiazole-based GABA or Glu receptor ligands.

To investigate the scope of substituted 3-hydroxyisothiazoles as carboxyl group bioisosteric units notably for the design of Glu receptor ligands, effective introduction of a range of aromatic and heteroaromatic substituents in the 5-position of protected 3-hydroxyisothiazole was identified as a key synthetic step. For the syntheses of this type of compounds, a transition-metal-catalyzed cross-coupling strategy was envisioned to be of particular interest. Apart from a regiospecific introduction of aryl substituents in the 5-position of 3,5-dichloroisothiazole-4-carbonitrile using a Suzuki coupling strategy,[12] Negishi or Suzuki cross-coupling reactions have, so far, not been reported using the isothiazole parental system, including *O*-protected 3-hydroxyisothiazoles. Substituents have usually been introduced either before cyclization[8,13] or via selective lithiation in the 5-position of 3-benzyloxyisothiazole **1**.[14] We here describe a convergent method

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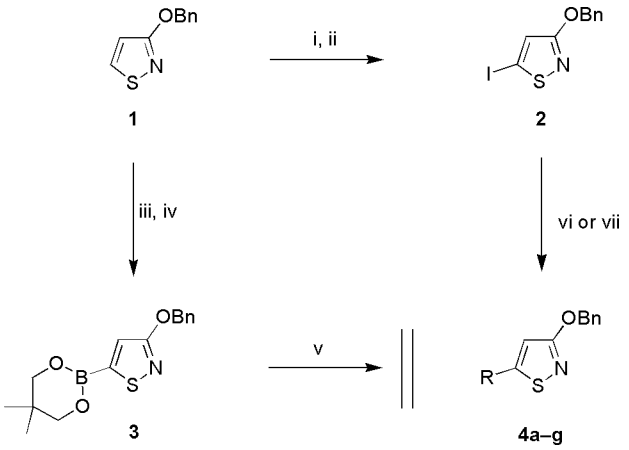
10.1021/jo035578g CCC: $27.50
Published on Web 01/21/2004

SCHEME 1[a]



[a] Key: (i) LDA, Et_2O; (ii) I_2, Et_2O; (iii) LDA, Et_2O, $B(O\text{-}i\text{-}Pr)_3$; (iv) AcOH, 2,2-dimethyl-1,3-propanediol; (v) Pd catalyst, phosphine ligand, base, solvent, electrophile; (vi) $PdCl_2(PPh_3)_2$, NEt_3, DME, H_2O, boron nucleophile; (vii) $PdCl_2(PPh_3)_2$, PPh_3, THF, DMF, zinc nucleophile.

for direct introduction of aromatic and heteroaromatic substituents into the 5-position of **1** (Scheme 1).

In principle, Negishi cross-coupling reactions involving readily available halides and a zinc halide of **1** would allow the direct introduction of aromatic or heteroaromatic substituents in a one-pot procedure. It was attempted to introduce the substituents using procedures analogous to those reported for the synthesis of thiazole and oxazole analogues.[15,16] Thus, the nucleophile was generated by selective lithiation of the 5-position of **1** using LDA in Et_2O,[14] followed by transmetalation at −78 °C using either $ZnCl_2$ or $ZnBr_2$. Various combinations of electrophiles, palladium catalysts, and phosphine ligands were used (for details see the Supporting Information). In all cases, major decomposition was observed, and less than 5% of the desired products were formed. The known limited thermal stability of the intermediate, 5-lithio-3-benzyloxyisothiazole,[14] may explain the low yields of product obtained.

To avoid transmetalation from the 5-lithiated species, a different strategy was pursued (Scheme 1). 3-Benzyloxy-5-iodoisothiazole **2** was prepared by selective lithiation in the 5-position of **1**[14] followed by addition of I_2 in Et_2O. A prerequisite for the formation of **2** in high yield (95%) is very slow addition of I_2. If the I_2 was added quickly, **2** was obtained in markedly lower yield (60%).

Introduction of Zn into **2** to provide a suitable intermediate for Negishi cross-coupling reactions was attempted following two different routes, either by direct insertion of Zn using activated Zn following a standard procedure[16,17] or by transmetalation of the corresponding Grignard intermediate with $ZnCl_2$ in analogy with earlier reported procedures.[18,19] Regardless of the method used for the preparation of the zincated species, less than 35% of product could be obtained in any of the Negishi cross-coupling reactions investigated (for details see the Supporting Information). In all reactions, the major product isolated was **1**, in which the iodide or zinc halide was replaced by hydrogen. The reason for this exhange has not been investigated, but it may be the results of either reduction of **2** mediated by Pd[20] or hydrolysis of the zincated species of **2**.

As Negishi cross-coupling reactions turned out not to be straightforward, a Suzuki cross-coupling strategy using the borate ester of **1** was envisioned as an alternative. Suzuki cross-coupling reactions can tolerate a wide range of functional groups[17] and are used extensively in organic synthesis. Boronic esters are normally stable, nonhygroscopic, and nontoxic[21] as compared to the trialkylstannyl derivatives used for Stille cross-coupling reactions.[22−24] 5-(5,5-Dimethyl[1,3,2]-2-dioxaborianyl)-3-benzyloxyisothiazole **3** was easily prepared in excellent yield by in situ trapping of the unstable 5-lithiated species, in analogy with an earlier report on similar compounds.[25] Suzuki cross-coupling reactions based on **3** were investigated using different electrophiles and various solvents or solvent combinations, palladium catalysts, phosphine ligands, and a wide range of bases (for details see the Supporting Information). In all reactions, deboronation was observed even at room temperature, and the major product isolated was **1**. As bulky electron-rich phosphine ligands have been reported to promote cross-coupling reactions[26] and reduce side reactions,[26,27] addition of different phosphine ligands was investigated, though without any improvements.

An explanation for the observed deboronation of **3** to **1** under the reaction conditions used may be instability of the otherwise shelf-stable **3** in certain solvents at elevated temperatures. Therefore, the stability of **3** was studied at reflux in the solvents used (for details see the Supporting Information), and within 2 h **1** was obtained as the major product in all protic solvents studied. Deboronation has previously been observed mainly for π-excessive heterocycles under alkaline conditions,[28] and hydrolytic deboronation has been observed in H_2O.[27] It has not been possible to completely avoid deboronation even when using dry and aprotic conditions.

Reversing the Suzuki cross-coupling reaction, and thereby the electronic properties using **2** as the electrophile, was investigated. Standard Suzuki cross-coupling reaction conditions[21,23] and a range of aromatic and heteroaromatic nucleophiles were studied. A suspension of **2** and $PdCl_2(PPh_3)_2$ in DME was stirred at room

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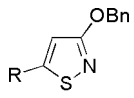
TABLE 1. Suzuki and Negishi Cross-Coupling Reactions Performed Using 2 as the Electrophile



4a–g

		isolated yield (%)	
product	R	Suzuki	Negishi
4a	phenyl	82	95
4b	2-thienyl	88	63
4c	3-thienyl	86	np[a]
4d	2-furyl	71	np
4e	2-pyridyl	np	48
4f	3-pyridyl	94	np
4g	4-pyridyl	69	np

[a] np: not performed.

temperature for 15 min, after which time the nucleophile, NEt_3, and H_2O were added, and the reaction was heated to 50 °C until disappearance of **2** as monitored by TLC. Using this procedure, it was possible to introduce π-electron rich as well as π-electron deficient substituents **4a**−**d**,**f**,**g** (Table 1). The isolated yields were good to excellent (69−94%), and hardly any homocouplings were observed. The reaction was quite robust, being neither water nor air sensitive except in a few cases in which the nucleophiles used were air sensitive.

A general drawback of the Suzuki cross-coupling reactions is the limited access of boronic acids or boronic esters of aromatic and heteroaromatic compounds. Thus, 3-benzyloxy-5-(2-pyridyl)isothiazole **4e** was not synthesized using the above-mentioned Suzuki reaction as no 2-substituted boron derivative of pyridine is commercially available. Instead, a Negishi-type reaction based on **2** as electrophilic reagent was examined (Scheme 1). In addition to 2-iodopyridine, iodobenzene and 2-bromothiophene were investigated in this Negishi cross-coupling reaction, representing π-deficient, "π-neutral", and π-excessive nucleophiles, respectively. A number of methods for creating the nucleophilic reagent were investigated, including lithiation followed by transmetalation to Zn,[15] oxidative insertion of previously activated Zn,[17] or transmetalation from the Grignard reagent.[18] Best results were obtained when the nucleophiles were generated using insertion of magnesium followed by transmetalation to Zn, after which time $PdCl_2(PPh_3)_2$, PPh_3, and **2** in THF solution were added, and the reaction was heated to 75 °C overnight. The conversion rates were good to excellent, affording the desired products **4a**,**b**,**e** in 48−95% yields (Table 1).

In conclusion, we have developed two methods for direct and convergent introduction of aromatic and heteroaromatic substituents into the 5-position of 3-benzyloxyisothiazole (**1**). The reactions studied are work-efficient, and the isolated yields are good to excellent. The two methods are complementary to one another as a wide range of functional groups are tolerated in Suzuki cross-coupling reactions, whereas a large number of commercially available halogen substituted aromatic and heteroaromatic compounds are known as possible reactants in the Negishi cross-coupling reactions.

Experimental Section

3-Benzyloxy-5-iodoisothiazole (2). Diisopropylamine (1.11 mL, 7.84 mmol) was dissolved in Et_2O (60 mL), and *n*-BuLi (4.90 mL, 1.6 M, 7.84 mmol) was added while stirring at −78 °C. After 20 min, 3-benzyloxyisothiazole **1**[14] (1.00 g, 5.23 mmol) in Et_2O (4.0 mL) was added dropwise, and the reaction was allowed to stir at −78 °C for 15 min. Iodine (1.59 g, 6.28 mmol) in Et_2O (35 mL) was added so slowly that the reaction did not turn red during the reaction. The reaction was allowed to warm to −40 °C. Saturated $NH_4Cl_{(aq)}$ was added, and the reaction was allowed to reach rt. The phases were separated and the aqueous phase extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and evaporated. CC (toluene/petroleum 1:1) afforded **2** as an oil (1.58 g, 4.98 mmol, 95%): ^{1}H NMR δ 7.46−7.30 (m, 5H), 6.77 (s, 1H), 5.36 (s, 2H); ^{13}C NMR δ 169.1, 136.3, 128.7, 128.4, 128.3, 112.4, 99.5, 70.6. Anal. Calcd for $C_{10}H_8INOS$: C, 37.87; H, 2.54; N, 4.42. Found: C, 38.10; H, 2.37; N, 4.39.

5-(5,5-Dimethyl[1,3,2]-2-dioxaborianyl)-3-benzyloxyisothiazole (3). *n*-BuLi (2.18 mL, 1.38 M, 3.0 mmol) was added to a solution of diisopropylamine (0.42 mL, 3.0 mmol) in Et_2O (22 mL) while stirring at −78 °C. After 20 min, B(O-*i*-Pr)$_3$ (0.92 mL, 4.0 mmol) was added, and the reaction was allowed to stir for 5 min at −78 °C before dropwise addition of **1** (382 mg, 2.0 mmol) in Et_2O (1.5 mL). The reaction was allowed to stir at −78 °C for 3.5 h, after which time the cooling bath was removed. After 15 min, glacial acetic acid (0.18 mL) was slowly added. 2,2-Dimethyl-1,3-propanediol (312 mg, 3.0 mmol) was added with stirring at rt. After 2.5 h,CH_2Cl_2 was added, and the resulting organic phase was washed with saturated $NH_4Cl_{(aq)}$, saturated $NaHCO_{3(aq)}$, and H_2O. Drying (Na_2SO_4) of the organic phase and evaporation of the solvent afforded crude **3** (540 mg, 1.78 mmol, 89%): ^{1}H NMR δ 7.50−7.32 (m, 5H), 6.90 (s, 1H), 5.41 (s, 2H), 3.76 (s, 4H), 1.03 (s, 6H); ^{13}C NMR δ 170.1, 148.8, 136.7, 128.5, 128.0, 117.8, 112.0, 72.4, 70.6, 32.0, 21.8. An analytical sample was recrystallized from Et_2O and petroleum (clear colorless crystals, mp 82−83 °C). Anal. Calcd for $C_{15}H_{18}BNO_3S$: C, 59.42; H, 5.98; N, 4.62. Found: C, 59.47; H, 6.12; N, 4.58.

General Procedure for Suzuki Cross-Coupling Reactions Using 2 as Electrophile. 3-Benzyloxyisothiazoles 4a−d,f,g. $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) was added to a solution of **2** (314 mg, 0.99 mmol) in DME (34 mL), and the reaction was stirred at rt for 15 min. NEt_3 (5.5 mL), the appropriate nucleophile (1.28 mmol), and H_2O (34 mL) were added. Stirring was continued at 50 °C until **2** disappeared. H_2O was added, and the mixture was extracted with Et_2O. The combined organic phases were washed with H_2O, 2 M $NaOH_{(aq)}$, and H_2O and then dried (Na_2SO_4) and evaporated to afford crude **4**.

3-Benzyloxy-5-phenylisothiazole (4a). The reaction was carried out as described in the general procedure using phenylboronic acid as nucleophile. The reaction was complete in 2 h. CC (toluene/petroleum 1:1) afforded **4a** as an oil, which crystallized upon standing to yield **4a** as clear colorless crystals (82%, mp 34−35 °C): ^{1}H NMR δ 7.57−7.32 (m, 10H), 6.82 (s, 1H) 5.43 (s, 2H); ^{13}C NMR δ 169.1, 167.3, 136.7, 131.2, 129.9, 129.3, 128.7, 128.4, 128.3, 126.3, 108.2, 70.3. Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.67; H, 4.97; N, 5.21.

3-Benzyloxy-5-(2-thienyl)isothiazole (4b). The reaction was carried out as described in the general procedure using 2-thienylboronic acid as nucleophile. The reaction was complete in 1 h. FC (toluene/petroleum 1:1) afforded **4b** as an oil (88%): ^{1}H NMR δ 7.47−7.33 (m, 6H), 7.25 (d, 1H, J = 3.5 Hz), 7.05 (dd, 1H, J = 5.2, 3.5 Hz), 6.69 (s, 1H), 5.41 (s, 2H); ^{13}C NMR δ 168.6, 159.6, 136.6, 133.1, 128.7, 128.31, 128.25, 128.23, 127.2, 126.3, 108.5, 70.4; HRMS calcd for $C_{14}H_{11}NOS_2$ 273.0282, found 273.0283 (+0.04 ppm). Anal. Calcd for $C_{14}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12. Found: C, 62.56; H, 4.18; N, 4.98.

3-Benzyloxy-5-(3-thienyl)isothiazole (4c). The reaction was carried out as described in the general procedure using 3-thienylboronic acid as nucleophile. The reaction was complete in 1.5 h. FC (toluene/petroleum 1:1) afforded **4c** as an oil (86%): ^{1}H NMR δ 7.48 (dd, 1H, J = 2.7, 1.1 Hz), 7.46−7.31 (m, 6H), 7.22 (dd, 1H, J = 5.0, 1.1 Hz), 6.69 (s, 1H), 5.40 (s, 2H); ^{13}C NMR δ 168.9, 161.3, 136.6, 132.1, 128.7, 128.3, 128.3, 127.2, 126.0,

123.0, 108.2, 70.4; HRMS calcd for $C_{14}H_{11}NOS_2$ 273.0282, found 273.0271 (−3.9 ppm). Anal. Calcd for $C_{14}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12. Found: C, 62.17; H, 4.05; N, 4.98.

3-Benzyloxy-5-(2-furyl)isothiazole (4d). The reaction was carried out as described in the general procedure using 2-furylboronic acid as nucleophile. The reaction was complete in 15 h. FC (toluene/petroleum 1:1) afforded **4d** as a yellow oil (71%): ^{1}H NMR δ 7.48−7.34 (m, 6H), 6.75 (s, 1H), 6.67 (d, 1H, J = 3.5 Hz), 6.50 (dd, 1H, J = 3.5, 1.8 Hz), 5.41 (s, 2H); ^{13}C NMR δ 168.3, 155.2, 145.9, 143.1, 136.2, 128.3, 128.0, 127.9, 111.8, 108.5, 106.4, 70.2; HRMS calcd for $C_{14}H_{11}NO_2S$ 257.0510, found 257.0527 (+6.6 ppm).

3-Benzyloxy-5-(3-pyridyl)isothiazole (4f). The reaction was carried out as described in the general procedure using 3-([1,3,2]-2-dioxaborianyl)pyridine as nucleophile. The reaction was complete in 1.5 h. CC (toluene/EtOAc 1:1) afforded **4f** as a brown oil that crystallized to light brown crystals upon standing (94%): ^{1}H NMR δ 8.83 (d, 1H, J = 1.8 Hz), 8.65 (dd, 1H, J = 5.3, 1.8 Hz), 7.83 (td, 1H, J = 8.2, 1.8 Hz), 7.50−7.35 (m, 6H), 6.87 (s, 1H), 5.44 (s, 2H); ^{13}C NMR δ 169.1, 163.3, 150.7, 147.1, 136.4, 133.5, 128.7, 128.4, 128.3, 127.4, 123.0, 109.3, 70.6; HRMS calcd for $C_{14}H_{11}N_2OS$ 268.0670, found 268.0665 (−1.9 ppm). An analytical sample was recrystallized from Et_2O and petroleum (mp 59−60 °C).

3-Benzyloxy-5-(4-pyridyl)isothiazole (4g). The reaction was carried out as described in the general procedure using 4-pyridylboronic acid as nucleophile. The reaction was complete in 2 h. CC (toluene/EtOAc 1:1) afforded **4g** as an oil that crystallized to light brown crystals upon standing (69%, mp 60−61 °C): ^{1}H NMR δ 8.70 (dd, 2H, J = 4.7, 1.8 Hz), 7.49−7.35 (m, 7H), 6.95 (s, 1H), 5.44 (s, 2H); ^{13}C NMR δ 169.1, 164.0, 150.9, 138.2, 136.3, 128.7, 128.4, 128.3, 120.4, 110.0, 70.7; HRMS calcd for $C_{14}H_{11}N_2OS$ 268.0670, found 268.0676 (+2.2 ppm). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 66.98; H, 4.53; N, 10.13.

General Procedure for Negishi Cross-Coupling Reactions Using 2 as Electrophile. 3-Benzyloxyisothiazoles 4a,b,e. (1) Generation of the Nucleophile. The aromatic or heteroaromatic halide (0.59 mmol) was added to a suspension of Mg (16 mg, 0.66 mmol) in THF (0.25 mL), and the reaction was heated to 50 °C for 1 h. The reaction was cooled to 0 °C, $ZnCl_2$ (90 mg, 0.66 mmol) was added, and the mixture was stirred at rt for 1 h.

(2) Negishi Cross-Coupling Reaction. A solution of **2** (168 mg, 0.53 mmol) in THF (1 mL), $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol), and PPh_3 (21 mg, 0.079 mmol) was added to the solution containing the nucleophile, and the mixture was heated to 75 °C for 15 h. H_2O was added, and the resulting mixture was extracted with CH_2Cl_2. Drying of the organic phases (Na_2SO_4) and evaporation gave crude **4**.

3-Benzyloxy-5-phenylisothiazole (4a). The reaction was carried out as described in the general procedure. However, a solution of PhMgCl (0.37 mL, 1.66 M in THF, 0.59 mmol) diluted with THF (1.5 mL) was used in the transmetalation reaction. CC (toluene/petroleum 1:1) afforded **4a** as a clear oil (95%), which crystallized upon standing. ^{1}H, ^{13}C, and mp were identical to **4a** isolated by Suzuki cross-coupling.

3-Benzyloxy-5-(2-thienyl)isothiazole (4b). The reaction was carried out as described in the general procedure. The nucleophile was generated using 2-bromothiophene. FC (toluene/petroleum 1:1) afforded **4b** (63%) with data identical to **4b** isolated by Suzuki cross-coupling.

3-Benzyloxy-5-(2-pyridyl)isothiazole (4e). The reaction was carried out as described in the general procedure. The nucleophile was generated using 2-iodopyridine. CC (toluene/EtOAc 1:1) afforded **4e** as an oil (48%): ^{1}H NMR δ 8.54 (bd, 1H, J = 4.7 Hz), 7.73−7.12 (m, 8H), 6.94 (s, 1H), 5.37 (s, 2H); ^{13}C NMR δ 167.3, 150.0, 137.2, 136.6, 132.4, 128.7, 128.5, 128.31, 128.26, 124.2, 119.6, 108.5, 70.4; HRMS calcd for $C_{14}H_{11}N_2OS$ 268.0670, found 268.0677 (+2.3 ppm).

Acknowledgment. We gratefully acknowledge the Mass Spectrometry Research Unit, University of Copenhagen, Denmark, for perfoming HRMS and the Analytical Research Department, H. Lundbeck A/S, Denmark, as well as the Department of Elemental Analysis, University of Copenhagen, Denmark, for perfoming elemental analyses.

Supporting Information Available: Procedures for the attempted cross-coupling reactions. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035578G