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Efficient Synthesis of Conjugated 1,3,4-Thiadiazole Hybrids through Palladium-Catalyzed Cross-Coupling of 2,5-Bis(4-bromophenyl)-1,3,4-thiadiazole with Boronic Acids

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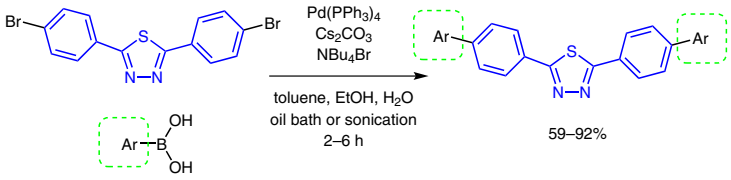

Ar = phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 4-pyridyl, 3-pyridyl

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Abstract New derivatives of 2,5-bis(4-heteroarylphenyl)-1,3,4-thiadiazole were synthesized under Suzuki cross-coupling reactions from 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole and commercially available boronic acids. Reactions were conducted in a two-phase solvent system in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0), cesium carbonate as a base, and tetrabutylammonium bromide playing a role of a phase-transfer catalyst.

Key words heterocycles, cross-coupling, phase-transfer catalysis, palladium, catalysis

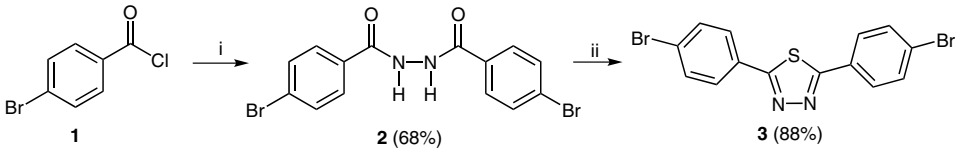
The thiadiazoles – a class of heterocyclic five-membered organic compounds containing two nitrogen atoms and a sulfur atom – exhibit high biological activity and therefore constitute an important group of compounds for use in medicine and agriculture.[1] From among all of the possible isomers of thiadiazole, chemists have focused on 1,3,4-thiadiazole and its derivatives.[2]

During the past twenty years, there has been a significant increase in interest in organic compounds exhibiting luminescent properties that may be applied in the production of efficient organic light-emitting diodes, scintillation counters, and optical brighteners.[3] An optimal organic luminophore is usually an extended π-conjugated chromophore system showing the proper electron-hole transporting properties, a high external quantum efficiency, and both thermal and chemical stability.[4] The literature indicates that, from the family of the five-membered heteroaromatic compounds commonly used in the production of new materials for optoelectronics, 1,3,4-oxadiazole derivatives have been intensively studied, for instance: 2-(4-biphenylyl)-5-(4-tertbutylphenyl)-1,3,4-oxadiazole (PBD),[5] 2,5-bis[2-(4-*tert*-butylphenyl)-1,3,4-oxadiazol-5-yl]pyridine (PDPyDP),[6] and 1,3,4-oxadiazole,2,2-(1,3-phenylene)bis{5-[4-(1,1-dimethylethyl)phenyl]} (OXD-7).[7] However, 1,3,4-thiadiazoles also exhibit interesting properties in this area.[8] A literature survey revealed examples of modification of luminophore electron-transporting properties by direct or indirect conjugation to other heteroaromatic systems such as pyridines, furans, thiophenes, selenophenes, tellurophenes, or 1,3,4-oxadiazoles.[9,10]

The most popular method for the synthesis of these heterocyclic compounds with substituents in positions 2 and 5 involves spontaneous cyclization and dehydration of *N*,*N*′-diacylhydrazines with diphosphorus pentasulfide[11] or Lawesson's reagent.[12] Other sources also describe exchange of the oxygen atom in the 1,3,4-oxadiazole to sulfur using thiourea,[13] and the cyclization of bithioureas[14] or thiosemicarbazides with other compounds containing a carbonyl group.[15]

In continuation of our scientific program on the application of acid hydrazides in the formation of selected heterocycles,[16,17] we decided to study the synthesis of conjugated 1,3,4-thiadiazole derivatives as 1,3,4-oxadiazole structural counterparts, conjugated via a phenylene linker to other homo- and heteroaromatic functionality such as benzene, pyridine, thiophene, and furan rings, hoping to obtain new potential monomers for optoelectronics. This issue seems to be very important due to the fact that electronic interactions in 1,3,4-thiadiazoles are relatively scarcely reported in the literature. One efficient approach features formation of the biaryl system via Suzuki cross-coupling, one of the most important catalytic methods of sp^2–sp^2 C–C construction.[18]

The work reported herein describes a convenient procedure for synthesizing novel, conjugated hybrids containing a 1,3,4-thiadiazole core from commercially available boronic acids and 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole.



Scheme 1 Synthesis of 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole (**3**) scaffold. *Reagents and conditions*: (i) $N_2H_4{\cdot}H_2O$, Et_3N, $CHCl_3$, r.t., 4 h; (ii) P_4S_{10}, xylene, reflux, 4 h.

The key structure 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole (**3**) was obtained according to a two-step procedure through intermediate the *N*,*N*′-diacylhydrazine **2**. Commercially available 4-bromobenzoyl chloride (**1**) was treated with hydrazine hydrate and triethylamine yielding the corresponding hydrazine derivative **2** (Scheme 1). Then the intermediate **2** underwent thionation by means of P_4S_{10} and subsequent cyclization in xylene solution at elevated temperature. The resulting compound **3**, representing the bifunctional precuror for the Suzuki cross-coupling reaction, was then subjected to reaction with a range of boronic acids in the presence of a palladium catalyst to obtain conjugated 1,3,4-thiadiazole derivatives.

In order to identify the optimal conditions, the phenylboronic acid (**4a**) was initially reacted with bifunctional dibromo derivative **3** in a mixture of polar solvents, such as water and ethanol, and gave the final product **5a** in a poor yield (3%, Table 1, entry 1). However, due to the low efficiency and problems with solubility it was decided to introduce a nonpolar solvent: toluene and a phase-transfer catalyst (NBu_4Cl, NBu_4Br). These operations led to noticeable improvements in yield (Table 1, entries 2 and 3). The next modifications comprised the use of various types of base to activate the boronic acid and to facilitate the transmetalation step. A range of metal carbonates – differing in cation size – was tested and this study showed that the cation of base had a moderate impact on the reaction yield (Table 1, entries 4–7) while the quantity of base played an important role (Table 1, entry 7 and 8). The best result was obtained using a small excess of phenylboronic acid (**4a**, Table 1, entry 9). In the final step, ultrasonication was applied and it was observed that, while maintaining the yield, the reaction time was considerably shortened (Table 1, entry 10).

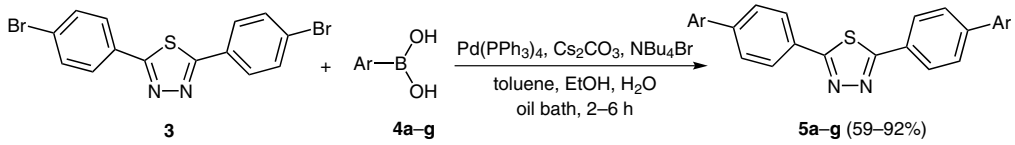
For these optimized conditions a series of reactions was carried out with different boronic acids to afford symmetrically substituted derivatives of 2,5-diphenyl-1,3,4-thiadiazole (Scheme 2). The starting compound **3** was treated with a variety of heteroaromatic boronic acids **4b**–**g** used in excess (1:2.5 molar ratio). The reaction mixture was heated in an oil-bath in the presence of the 5 mol% palladium catalyst $Pd(PPh_3)_4$ and 10 mol% NBu_4Br as the phase-transfer catalyst, using the two-phase, three-component solvent system (EtOH–H_2O–toluene). The base employed in the reaction was Cs_2CO_3 containing the largest cation, because it gave the best results in the synthesis of optimized 1,3,4-thiadiazole derivative **5a**.[21]

This study resulted in novel symmetrical 2,5-diphenyl-1,3,4-thiadiazole derivatives **5a**–**g** substituted at the position 4 of the phenylene linker with phenyl and heteroaryl groups in high yields (59–92%, Table 2). The new products were characterized by elemental analysis and spectroscopic methods. UV/Vis spectra measurements of the investigated

Table 1 Optimization of the Coupling Reaction to Obtain **5a**

Entry	**3**/**4a** ratio (equiv)	Solvents	PTC catalyst (equiv)	Catalyst $Pd(PPh_3)_4$ (equiv)	Base (equiv)	Reaction time (h)	Yield (%)[a]
1	1:2	EtOH–H_2O	–	0.01	K_2CO_3 (5)	5	3[b]
2	1:2	EtOH–H_2O–toluene	NBu_4Cl (0.1)	0.01	K_2CO_3 (5)	5	29[b]
3	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.01	K_2CO_3 (5)	5	35[b]
4	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	K_2CO_3 (5)	5	50[b]
5	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Li_2CO_3 (5)	5	47[b]
6	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Na_2CO_3 (5)	5	48[b]
7	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Cs_2CO_3 (5)	5	51[b]
8	1:2	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Cs_2CO_3 (10)	5	60[b]
9	1:2.5	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Cs_2CO_3 (10)	5	92[b]
10	1:2.5	EtOH–H_2O–toluene	NBu_4Br (0.1)	0.05	Cs_2CO_3 (10)	2	91[c]

[a] Yield with respect to the starting 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole (**3**).
[a] Conditions: reaction temperature 80 °C (oil bath).
[b] Conditions: ultrasonic bath.



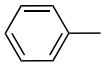
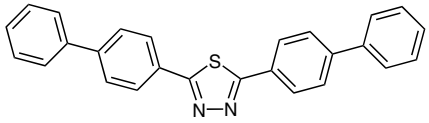
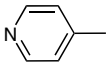
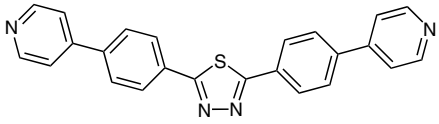
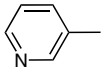
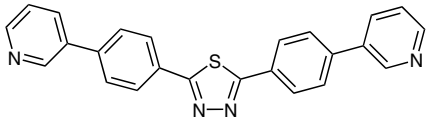
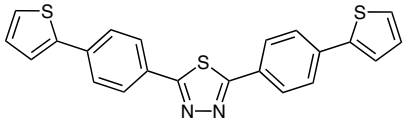
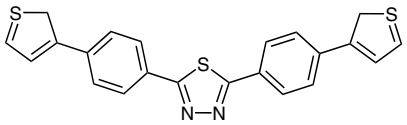
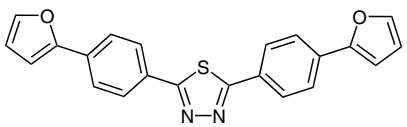
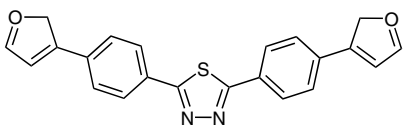
Ar = phenyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 4-pyridyl, 3-pyridyl

Scheme 2 Synthesis of 2,5-bis(4-arylphenyl)-1,3,4-thiadiazole **5a**–**g** hybrids. *Reagents and conditions*: bifunctional dibromo derivative **3** (1.00 mmol), boronic acid **4** (2.50 mmol), $Pd(PPh_3)_4$ (0.05 mmol), TBAB (0.10 mmol), Cs_2CO_3 (10 mmol), toluene–H_2O–EtOH (10:6:3 mL), 80 °C (oil bath), 2–6 h.

compounds registered in CH_2Cl_2 showed the presence of two or three absorption maxima depending on the nature of the terminal aryl group (see Supporting Information). The five-membered heterocyclic terminal substituents **5d**–**g** present in the studied hybrids were shifted bathochromically by 5 to 23 nm (λ_{max} = 340–358 nm), in contrast to the model 3,5-bis(4-biphenylyl)-1,3,4-thiadiazole (**5a**, λ_{max} = 335 nm); while for the pyridine derivatives **5b**,**c** (λ_{max} = 330 nm) the reversed trend was observed. The fluorescence spectra were composed of three individual signals. However, the Stokes' shifts (Δ) were relatively small which testifies to the slight change in geometry of the molecules during the transition from the ground state to the first excited state. Generally, the absorption maxima of the studied 1,3,4-thiadiazoles were red-shifted (11–25 nm) in contrast to their 1,3,4-oxadiazole counterparts.[19]

The reported methodology demonstrates an efficient way to synthesize extended derivatives of 1,3,4-thiadiazoles

Table 2 Synthesis of 2,5-Bis(4-arylphenyl)-1,3,4-oxadiazoles **5a**–**g** in Suzuki Cross-Coupling Reactions

Compd **5**	Substituent $ArB(OH)_2$	Reaction time (h)	Mp (°C)	Product	Yield (%)
5a		5	296–298 (lit.20 294–296 °C)		92
5b		4	251–253 (decomp.)		84
5c		5	241–243 (decomp.)		87
5d		2	270–272 (decomp.)		65
5e		4	329–332 (decomp.)		87
5f		4	227–228 (decomp.)		59
5g		6	280–282 (decomp.)		77

substituted symmetrically with a range of heteroaromatic arrangements via a 1,4-phenylene linker at positions 2 and 5. The bifunctional precursor: 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole that was readily prepared from acyclic *N,N'*-diacylhydrazines underwent Suzuki cross-coupling reactions in the presence of palladium catalyst both under conventional and ultrasound-assisted conditions. The present protocol may be particularly useful in the synthesis of monomers for linear conjugated systems that may find potential application in materials science.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378826.

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(21) **Representative Procedure for Suzuki Coupling**

2,5-Bis(4-bromophenyl)-1,3,4-thiadiazole (**3**, 0.40 g, 1.00 mmol), the appropriate boronic acid (2.50 mmol), tetrakis(triphenylphosphine)palladium(0) (0.06 g, 0.05 mmol), TBAB (0.03 g, 0.10 mmol), and Cs_2CO_3 (3.26 g, 10.00 mmol) were treated with a combination of toluene (10 mL), H_2O (6 mL), and EtOH (3 mL). The mixture was heated to 80 °C (oil bath) for 2–6 h (TLC monitoring). After cooling, $CHCl_3$ (200 mL) was added and the mixture filtered through silica gel (20 mL). The filtrate was separated, the organic layer was dried over $MgSO_4$ and then concentrated on a rotary evaporator. The residue was treated with a mixture of benzene–EtOAc (3:1). The solid precipitate was filtered off, washed with benzene–EtOAc (3:1) and air-dried to give the pure 2,5-disubstituted 1,3,4-thiadiazole.

3,5-Bis(4-biphenylyl)-1,3,4-thiadiazole (5a)

White-pearl solid (0.34 g, 92% yield); mp 296–298 °C (lit.[16] 294–296 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.66 (d, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 8.11 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 124.4, 127.1, 127.8, 128.1, 128.4, 129.0, 139.9, 143.9, 167.8. UV/Vis: λ_{max} ($CHCl_3$) 335.0 nm (ε · 10^{-3} 60.3 cm^{-1} M^{-1}). IR (ATR): ν = 3060, 3037, 2162, 1946, 1821, 1675, 1604, 1561, 1488, 1451, 1432, 1420, 1401, 1316, 1253, 1185, 1170, 1100, 1040, 1027, 1005, 997, 988, 910, 838, 760,718, 684 cm^{-1}. Anal. Calcd for $C_{26}H_{18}N_2S$: C, 79.97; H, 4.65; N, 7.17. Found: C, 79.99; H, 4.63; N, 7.21. HRMS: *m/z* calcd for [$C_{26}H_{18}N_2S$ + H^+]: 391.1269; found: 391.1267.