SYNTHESIS OF 3-ALKYL-4-ARYL- AND 3,4-DIARYL-1,2,5-THIADIAZOLES *VIA* PALLADIUM-CATALYZED CROSS-COUPLING REACTION

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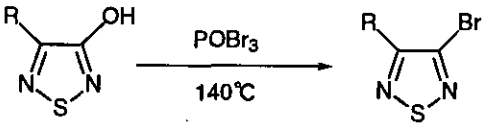
Abstract — 4-Substituted 3-aryl-1,2,5-thiadiazoles were synthesized by palladium-catalyzed cross-coupling reaction of arylstannane with easily available 4-substituted 3-halogeno- and 3-trifluoromethylsulfonyloxy-1,2,5-thiadiazoles.

Compounds containing the 1,2,5-thiadiazole ring system are known to elicit a wide range of biological activity.[1] Recently, we have reported that a series of 1,2,5-thiadiazole derivatives were highly potent and specific inhibitors of human immunodeficiency virus type 1 (HIV-1).[2] In addition to the biological activity, these compounds have also been found to possess chemical usefulness. It is known that reduction of 3,4-disubstituted 1,2,5-thiadiazoles lead to 1,2-diamines which play key roles in coordination chemistry and asymmetric catalysis.[1,3] Although 3,4-disubstituted 1,2,5-thiadiazoles have been prepared using N_4S_4 cyclization reactions[1,4] and by treatment of S_2Cl_2 with 1,2-diamines,[1,5] these are not necessarily general methods: the yields are low, N_4S_4 has explosive,[6] and 1,2-diamines are not readily available. An alternative strategy for the synthesis of 3,4-disubstituted 1,2,5-thiadiazoles seemed to be the palladium-mediated cross-coupling methodology.[7]

We now report that the coupling reaction of 4-substituted 3-halogeno- and 3-trifluoromethylsulfonyloxy-1,2,5-thiadiazoles with arylstannanes takes place in the presence of palladium catalysts to give 4-substituted 3-aryl-1,2,5-thiadiazoles in good yields. A series of 4-substituted 3-bromo-1,2,5-thiadiazoles were synthesized in good yields by bromination of 4-substituted 3-hydroxy-1,2,5-thiadiazoles which were prepared by literature methods,[5] as shown in Table 1. It is known that 1,2,5-thiadiazole (**1**) reacts with

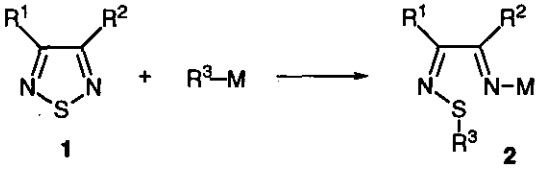
organometalic reagents, R^3-M, such as Grignard reagents and alkyllithium reagents to give ring opening products (**2**) (Scheme 1).[1,8]

Table 1 . Synthesis of 4-Substituted 3-Bromo-1,2,5-thiadiazoles



Entry	R	Yield(%)
1	Ph	80
2	4-ClPh	81
3	2,6-Cl_2Ph	65
4	*tert*-Bu	71

Scheme 1

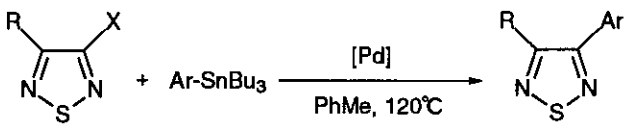


1 **2**

Therefore, to avoid the ring opening, we carried out the reaction of 4-substituted 3-bromo-1,2,5-thiadiazole with tributylarylstannanes in the presence of palladium catalysts under nitrogen in toluene at 120 °C and prepared 4-substituted 3-aryl-1,2,5-thiadiazoles in good yields. These results are summarized in Table 2. Interestigly, this arylation proceeded even using 3-chloro-4-phenyl-1,2,5-thiadiazole as substrate, which was prepared from 2-amino-2-phenylacetonitrile with sulfur monochloride, although the yields were low and the large amount of substrate was recovered (Table 2, Entries 1 and 2). This result indicates that 3-chlorine of the 1,2,5-thiadiazole skeleton is activated to some extent in comparison with chlorobenzene. The yield of coupling products was improved by using 3-bromo-4-phenyl-1,2,5-thiadiazole in the presence of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ (Table 2, Entries 3 and 4). Although $Pd(PPh_3)_4$ was more effective than $PdCl_2(PPh_3)_2$ in the cross-coupling of 3-chloro-4-phenyl-1,2,5-thiadiazole with tributyl(4-chlorophenyl)stannane (Table 2, Entries 1 and 2), both these catalysts were effective in the reaction using

3-bromo-4-phenyl-1,2,5-thiadiazole as substrate (Table 2, Entries 3 and 4). Appling the same conditions to sterically hindered substrates were successful and the desired products were obtained in moderate yields (Table 2, Entries 6-10). However, starting material was recovered and a trace amount of Ph_3PS and 2,6-dichlorobenzonitrile arising from 3-bromo-4-(2,6-dichlorophenyl)-1,2,5-thiadiazole were obtained (Table 2, Entries 6-9). It is likely that the formation of byproducts is due to the reductive ring opening of 1,2,5-thiadiazole nucleus with Pd(0) at high temperature and thus the activity of catalyst is lost. As acceleration of Still reaction by the addition of LiCl has been reported,[7] the effect of LiCl was studied in this cross-coupling reaction.

Table 2 . Synthesis of 4-Substituted 3-Aryl-1,2,5-thiadiazoles



Entry	R	X	Ar	[Pd][a]	Yield(%)
1	Ph	Cl	4-ClPh	$Pd(PPh_3)_4$	37
2	Ph	Cl	4-ClPh	$PdCl_2(PPh_3)_2$	7
3	Ph	Br	4-ClPh	$Pd(PPh_3)_4$	89
4	Ph	Br	4-ClPh	$PdCl_2(PPh_3)_2$	90
5	Ph	Br	4-MeOPh	$Pd(PPh_3)_4$	92
6	2,6-Cl_2Ph	Br	Ph	$Pd(PPh_3)_4$	78
7	2,6-Cl_2Ph	Br	4-MePh	$Pd(PPh_3)_4$	51
8	2,6-Cl_2Ph	Br	4-MeOPh	$Pd(PPh_3)_4$	76
9	2,6-Cl_2Ph	Br	4-ClPh	$Pd(PPh_3)_4$	51
10	*tert*-Bu	Br	4-ClPh	$Pd(PPh_3)_4$	86
11[b]	Ph	TfO	4-ClPh	$PdCl_2(PPh_3)_2$	83
12[c]	Ph	TfO	4-ClPh	$PdCl_2(PPh_3)_2$	56

a) 5 mol%. b) In the presence of LiCl. c) In the absence of LiCl.

As a result, it was found that this cross-coupling reaction using 4-phenyl-3-trifluoromethylsulfonyloxy-1,2,5-thiadiazole as substrate was enhanced by the addition of LiCl (Table 2, Entry 11), although this reaction proceeded smoothly in the absence of LiCl (Table 2, Entry 12).

In conclusion, this work provides a general synthesis of a variety of 3-alkyl-4-aryl- and 3,4-diaryl-1,2,5-thiadiazoles.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded on a JASCO ir-810 spectrophotometer as potassiun bromide pellets or as liquid films on sodium chloride plates. ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini-200 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed on a Yanaco mt-3 elemental analyzer. Column chromatography was carried out on Wako gel C-300.

General Procedure for the Preparation of the Bromides (Table 1).

3-Bromo-4-phenyl-1,2,5-thiadiazole (Entry 1). A mixture of 3-hydroxy-4-phenyl-1,2,5-thiadiazole (17.82 g, 0.1 mol) and $POBr_3$ (57.33 g, 0.2 mol) was stirred at 160 °C under nitrogen for 12 h. The mixture was cooled to room temperature. Water was added to the mixture, which was extracted with diethyl ether. The ethereal extract was washed successively with 1% aqueous sodium hydroxide solution, water, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane to give the 3-bromo-4-phenyl-1,2,5-thiadiazole (19.29 g, 80 %): mp 59 - 60 °C (from hexane) (lit.,[4c] 56 - 57 °C).

3-Bromo-4-(4-chlorophenyl)-1,2,5-thiadiazole (Entry 2). mp 60 - 61 °C (from hexane); ^1H nmr (200 MHz, $CDCl_3$) δ 7.45 - 7.55 (m, 2H), 7.85 - 7.95 (m, 2H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 129.1, 129.7, 130.5, 131.7, 136.7, 159.6; ir (KBr, cm^{-1}) ν_{max} 1455, 1350, 1145, 1090, 965, 820. Anal. Calcd for $C_8H_4N_2BrClS$: C, 34.87; H, 1.46; N, 10.17. Found: C, 34.71; H, 1.64; N, 10.28.

3-Bromo-4-(2,6-dichlorophenyl)-1,2,5-thiadiazole (Entry 3). mp 63 - 64 °C (from hexane); ^1H nmr (200 MHz, $CDCl_3$) δ 7.35 - 7.55 (m); ^{13}C nmr (50 MHz, $CDCl_3$) δ 128.4, 130.2, 132.0, 134.5, 135.9, 158.0; ir (KBr, cm^{-1}) ν_{max} 1430, 1345, 1165, 965, 785. Anal. Calcd for $C_8H_3N_2BrCl_2S$: C, 31.00; H, 0.98; N, 9.04. Found: C, 30.93; H, 0.89; N, 8.98.

3-Bromo-4-*tert*-butyl-1,2,5-thiadiazole (Entry 4). oil; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.52 (s); ^{13}C nmr (50 MHz, $CDCl_3$) δ 28.8, 36.4, 130.8, 169.1; ir (neat, cm^{-1}) ν_{max} 2970, 1480, 1365, 1330, 1185, 1010, 845, 820. Anal. Calcd for $C_6H_9N_2BrS$: C, 32.59; H, 4.10; N, 12.67. Found: C, 32.44; H, 4.28; N, 12.78.

General Procedure for the Preparation of the 3-Alkyl-4-Aryl- and 3,4-Diaryl-1,2,5-thiadiazoles (Table 2).

From 4-Substituted 3-Halogeno-1,2,5-thiadiazoles

3-(4-Chlorophenyl)-4-phenyl-1,2,5-thiadiazole (Entry 3). A mixture of 3-bromo-4-phenyl-1,2,5-thiadiazole (723 mg, 3 mmol), tributyl(4-chlorophenyl)stannane (1.325 g, 3.3mmol), and $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) in toluene (15 ml) was stirred at 120 °C under nitrogen for 12 h. The mixture was cooled to room temperature, poured into potassium fluoride solution, and extracted with ether. The ethereal extract was successively washed with 1% aqueous sodium hydroxide solution, water, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane/chloroform (2/1) to give the 3-(4-chlorophenyl)-4-phenyl-1,2,5-thiadiazole (728 mg, 89 %): mp 61 - 62 °C (from hexane) (lit.,[4a] 62 - 63 °C).

3-(4-Methoxyphenyl)-4-phenyl-1,2,5-thiadiazole (Entry 5). mp 66 - 67 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.90 (d, J=9.0 Hz, 2H), 7.35 - 7.60 (m, 7H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 55.5, 114.2, 125.9, 128.8, 129.3, 129.5, 130.7, 133.8, 159.90, 159.91, 160.7; ir (KBr, cm^{-1}) ν_{max} 1610, 1520, 1400, 1300, 1260, 1245, 1170, 825. Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 66.94; H, 4.32; N, 10.72.

3-(2,6-Dichlorophenyl)-4-phenyl-1,2,5-thiadiazole (Entry 6). mp 63 - 66 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.25 - 7.65 (m); ^{13}C nmr (50 MHz, $CDCl_3$) δ 127.9, 128.6, 128.9, 129.9, 131.4, 132.4, 132.9, 135.7, 155.3, 160.7; ir (KBr, cm^{-1}) ν_{max} 1560, 1425, 1380, 1190, 960, 775. Anal. Calcd for $C_{14}H_8N_2Cl_2S$: C, 54.74; H, 2.62; N, 9.12. Found: C, 54.58; H, 2.44; N, 9.40.

3-(2,6-Dichlorophenyl)-4-(4-tolyl)-1,2,5-thiadiazole (Entry 7). mp 122 - 126 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.14 (d, J=7.9 Hz, 2H), 7.3 - 7.5 (m, 5H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 21.5 127.8, 128.6, 129.6, 131.3, 133.0, 135.7, 140.0, 155.2, 160.7; ir (KBr, cm^{-1}) ν_{max} 1560, 1430, 1380, 1195, 960, 820, 790, 775. Anal. Calcd for $C_{15}H_{10}N_2Cl_2S$: C, 56.09; H, 3.14; N, 8.72. Found: C, 55.89; H, 2.95; N, 9.00.

3-(2,6-Dichlorophenyl)-4-(4-methoxyphenyl)-1,2,5-thiadiazole (Entry 8). mp 135 - 139 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.85 (d, J=8.8 Hz, 2H), 7.35 - 7.55 (m, 5H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 55.4, 114.3, 125.1, 128.6, 129.3, 131.3, 133.1, 135.8, 154.9, 160.3, 160.9; ir (KBr, cm^{-1}) ν_{max} 1605, 1425, 1260, 1245, 1170, 1020, 830, 825, 790. Anal. Calcd for $C_{15}H_{10}N_2OCl_2S$: C, 53.43; H, 2.99; N, 8.31. Found: C, 53.23; H, 2.80; N, 8.59.

3-(2,6-Dichlorophenyl)-4-(4-chlorophenyl)-1,2,5-thiadiazole (Entry 9). mp 109 - 111 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.25 - 7.55 (m); ^{13}C nmr (50 MHz, $CDCl_3$) δ 128.7, 129.20, 129.22, 130.9, 131.6, 132.5, 135.7, 136.1, 155.2, 159.5; ir (KBr, cm^{-1}) ν_{max} 1430, 1385, 1090, 960, 835, 825, 790, 780. Anal. Calcd for $C_{14}H_7N_2Cl_3S$: C, 49.22; H, 2.07; N, 8.20. Found: C, 49.02; H, 1.88; N, 8.48.

3-(4-Chlorophenyl)-4-*tert*-butyl-1,2,5-thiadiazole (10). mp 49 - 51 °C (from hexane); ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.29 (s, 9H), 7.31 (d, J=8.7 Hz, 2H), 7.43 (d, J=8.7 Hz, 2H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 30.6, 36.6, 128.6, 131.0, 135.0, 135.3, 160.1, 170.8; ir (KBr, cm^{-1}) ν_{max} 2960, 1500, 1395, 1145, 1090, 990, 825, 815. Anal. Calcd for $C_{12}H_{13}N_2ClS$: C, 57.02; H, 5.18; N, 11.08. Found: C, 56.82; H, 5.00; N, 11.36.

From 4-phenyl-3-trifluoromethylsulfonyloxy-1,2,5-thiadiazole

3-(4-Chlorophenyl)-4-phenyl-1,2,5-thiadiazole (Entry 11). A mixture of 4-phenyl-3-trifluoromethylsulfonyloxy-1,2,5-thiadiazole (310 mg, 1 mmol), tributyl(4-chlorophenyl)stannane (442 mg, 1.1 mmol), LiCl (212 mg, 5 mmol), and $Pd(PPh_3)_4$ (36 mg, 0.05 mmol) in toluene (10 ml) was stirred at 120 °C under nitrogen for 12 h. The mixture was cooled to room temperature, poured into water, and extracted with ether. The ethereal extract was successively washed with 1% aqueous sodium hydroxide solution, water, and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane/chloroform (2/1) to give the 3-(4-chlorophenyl)-4-phenyl-1,2,5-thiadiazole (226 mg, 83%): mp 61 - 62 °C (from hexane) (lit.,[4a] 62 - 63 °C).

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