Synthesis of Unsymmetrical 3,6-Disubstituted Pyridazines. A Palladium-Catalyzed Approach from 3-Iodopyridazines†

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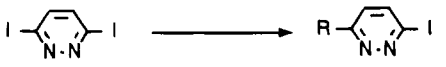
The pyridazine ring has demonstrated many synthetic[1] and several biological uses.[2] Despite the useful nature of pyridazines, there are a limited number of synthetic approaches to substitution on these electron deficient rings, and functionalization of the pyridazine nucleus continues to be of synthetic interest.[3,4] In this paper, we describe an efficient approach to 3,6-disubstituted pyridazines through use of 3-iodo-6-substituted pyridazines in a variety of palladium-catalyzed coupling reactions.

The use of palladium-catalyzed coupling of pyridazines has been limited to alkynes.[4,5] In general, 3-chloropyridazines have been employed as substrates in these reactions,[5,6] and harsh conditions have often resulted in unacceptably low yields. In the only case where a 3-iodopyridazine has been used, 3-iodo-6-methylpyridazine has been reported to undergo coupling with acetylenes in only 30–48% yields.[5] In a recent report,[4] 3-(trifluoromethanesulfonyl)pyridazines were utilized effectively under very mild conditions. The major drawback to this procedure is the cost and limited availability of commercially available starting pyridazinones. In most cases, the requisite pyridazinones are only available through synthesis. We felt that these complications could be obviated by iodination of inexpensive, commercially available 3,6-dichloropyridazine.

Recently, it has been stated that iodopyridazines were "not easily accessible."[4] We have found that generalization misleading. In this work, the requisite 3,6-diiodopyridazine was obtained straightforwardly from 3,6-dichloropyridazine using a reported procedure.[7] Nucleophilic substitution by methoxide,[7] fluoride, dimethylamine, and thiomethoxide afforded iodopyridazines **1a–d** in good to excellent yields (Table 1). Disubstitution by the nucleophile was never observed.

Alkynyl coupling with pyridazines **1a–c** using either propargyl alcohol or phenylacetylene at room temperature using standard methodology provided products in good yield as shown in Table 2. Of particular note is the reaction of **1a** with phenylacetylene at room temperature to form **3a** in 67% yield. In a previous approach, **3a** was obtained in 49% yield only after heating 3-chloro-6-methoxypyridazine and phenylacetylene in Et_2NH with $CuI/PdCl_2(PPh_3)_2$ at 70 °C for 24 h.[5] Additionally, coupling **1a** with propynylphenyl ether[8] afforded alkynylpyridazine **4** quantitatively (Scheme 1). Catalytic reduction of **4** provided the phenyloxypropyl pyridazine **5** in 70% overall yield.

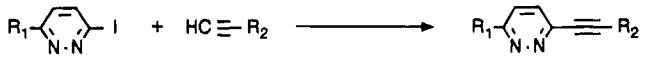
Table 1. Preparation of 3-Substituted 6-Iodopyridazines 1a–d



1a-d

compd	R	condns	% yield	mp, °C
1a[5]	–OMe	NaOMe/MeOH, reflux, 12 h	92	99–100
1b	–F	KF/DMSO, 120 °C, 18 h	90	118–120
1c	$-NMe_2$	aqueous Me_2NH, EtOH, reflux, 12 h	99	132–134
1d	–SMe	NaSMe/EtOH, reflux, 12 h	67	116–118

Table 2. Alkynyl Cross-Coupling with Iodopyridazines 1a–c



1a-c **2a-c, 3a, 3c**

pyridazine	R_1	R_2	% yield	mp, °C
2a	–OMe	$-CH_2OH$	93	140 dec
2b	–F	$-CH_2OH$	64	86–88
2c	$-NMe_2$	$-CH_2OH$	85	108–110
3a	–OMe	–Ph	67	96–98[a]
3c	$-NMe_2$	–Ph	85	146–148

[a] Lit. mp 98 °C.[5]

To further explore the utility of these 3-iodopyridazines in palladium-catalyzed cross-couplings, **1a**, **1c**, and **1d** were reacted with heteroarylstannanes under conditions previously developed in these laboratories.[9] In Table 3, reaction of **1a**, **1c**, and **1d** with 2-(tributylstannyl)-thiophene[10] provided the thiophene coupled heterobiaryls **6a**, **6c**, and **6d** in good yield. Reaction of **1a** and **1c** with 2-[5-[5-(trimethylstannyl)]furyl]-1,3-dioxolane[11] afforded the furyl coupled pyridazines **7a** and **7c** in 81 and 85% yields, respectively. Alternatively, Suzuki coupling[12] of **1a** and **1c** with phenylboronic acid afforded **8a** and **8c** in good yield as shown in Table 4. To our knowledge, these examples are the first reports of palladium-catalyzed biaryl coupling with pyridazines.

Starting from commercially available 3,6-dichloropyridazine, we have demonstrated that unsymmetrical 3,6-disubstituted pyridazines may be prepared in a mild, efficient manner via three simple steps: diiodination, nucleophilic substitution, and a palladium-catalyzed coupling. This methodology should prove useful in preparing many biologically interesting substituted pyridazines.

† This work was performed at the Sterling Winthrop Pharmaceuticals Research Division prior to its purchase by Sanofi.

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(11) Synthesized according to the following with the exception that trimethylstannyl chloride was substituted for tributylstannyl chloride: Yamamoto, M.; Yamada, K.; Izukawa, H.; Satki, M. *J. Chem. Soc., Chem. Commun.* **1988**, 561.
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Scheme 1

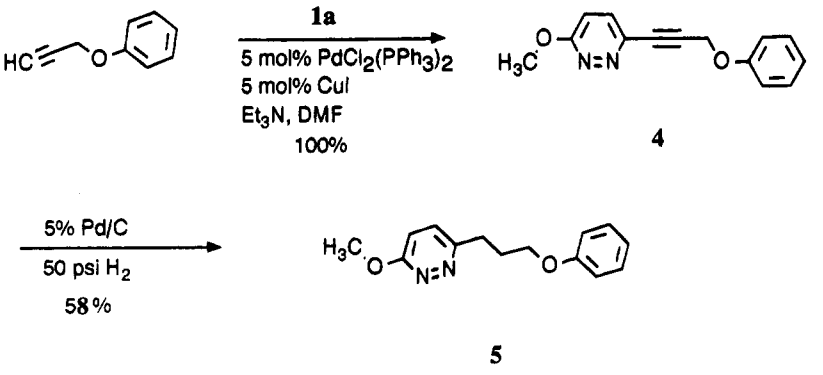
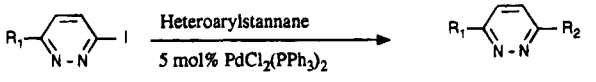
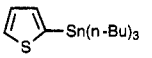
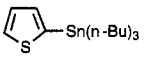
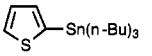
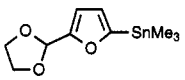
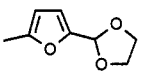
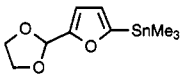
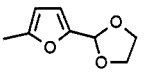


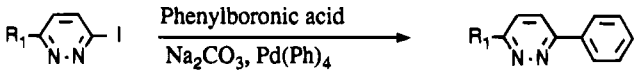
Table 3. Heterobiaryl Cross-Coupling of Pyridazines 1a, 1c, and 1d



pyridazine	stannane	R_1	R_2	% yield	mp, °C
6a[a]		−OMe		93	73−74
6c[a]		$-NMe_2$		77	120−122
6d[a]		−SMe		75	102−104
7a[b]		−OMe		81	95−97
7c[b]		$-NMe_2$		85	101−103

[a] DMF, 80 °C. [b] THF, reflux.

Table 4. Arylboronic Acid Cross-Coupling with Pyridazines 1a and 1c



pyridazine	R_1	% yield	mp, °C
8a	−OMe	76	110−112
8c	$-NMe_2$	58	115−116

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. NMR spectra were obtained using either a General Electric QE-300 or Bruker-AC200 FTNMR. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Preparative chromatography was performed using a Büchi B680 MPLC system connected to an ISCO UV detector and fraction collector. All reported melting points are of solids recrystallized from isopropyl acetate/hexanes. The solvents THF, CH_2Cl_2, toluene, and DMF were dried over molecular sieves. Anhydrous diethyl ether was purchased from Mallinckrodt and used without further purification. Organic extracts were dried over $MgSO_4$.

3-Fluoro-6-Iodopyridazine (1b). A mixture of 3,6-diiodopyridazine[7] (5.0 g, 15 mmol) in DMSO (20 mL) and 0.6 g of KF was heated to 140 °C for 18 h. The reaction was allowed to come to rt and diluted with H_2O (60 mL). Extracted with EtOAc (75 mL), the organic layer was washed with H_2O (5 × 100 mL) and concentrated in vacuo to yield 2.6 g (90%) of product as a tan solid: mp 118−120 °C; ^1H NMR ($CDCl_3$) δ 6.98 (dd, J_{HH} = 9.3 Hz, J_{HF} = 1.7 Hz, 1H), 7.95 (dd, J_{HH} = 9.3 Hz, J_{HF} = 7.0 Hz, 1H). Anal. Calcd for $C_4H_2FIN_2$: C, 21.45; H, 0.90, N, 12.51. Found: C, 21.92; H, 0.86; N, 12.24.

3-(Dimethylamino)-6-iodopyridazine (1c). To 5.0 g (15 mmol) of 3,6-diiodopyridazine[7] in 20 mL of EtOH was added 2.5 mL of 40% aqueous dimethylamine, and the solution was heated to reflux for 12 h. The reaction was allowed to cool to room temperature, and the solvent was removed in vacuo. The residue was then diluted with H_2O (40 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (3 × 50 mL). The solvent was removed in vacuo to yield 3.6 g (99%) of product as a yellow solid: mp 132−134 °C; ^1H NMR ($CDCl_3$) δ 3.1 (s, 6H), 6.5 (d, J = 9.4 Hz, 1H), 7.4 (d, J = 9.4 Hz, 1H). Anal. Calcd for $C_6H_8N_3I$: C, 28.93; H, 3.24; N, 16.87. Found: C, 29.20; H, 3.17; N, 16.88.

3-Iodo-6-(methylthio)pyridazine (1d). To 0.50 g (1.5 mmol) of 3,6-diiodopyridazine[7] in 5 mL of EtOH was added 0.11 g (1.6 mmol) of sodium thiomethoxide and was heated to reflux for 12 h. The reaction was allowed to come to rt, and the solvent was removed in vacuo. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL). The organic layer was washed with H_2O (3 × 10 mL). Concentration in vacuo provided 0.26 g (67%) of product as a light tan solid: mp 116−118 °C; ^1H NMR ($CDCl_3$) δ 2.6 (s, 3H), 7.0 (d, J = 8.4 Hz, 1H), 7.5 (d, J = 8.4 Hz, 1H). Anal. Calcd for $C_5H_5IN_2S$: C, 23.82; H, 2.00; N, 11.11. Found: C, 24.11; H, 2.15; N, 10.93.

General Procedure for Coupling Propargyl Alcohol with 1a-c. 3-[3-(6-Methoxypyridazinyl)]-2-propyn-1-ol (2a). To 0.3 g (1.3 mmol) of 3-methoxy-6-iodopyridazine (**1a**) in 3 mL of THF was added 0.1 mL (1.4 mmol) of propargyl alcohol, 0.5 mL of Et_3N (6.8 mmol), 7 mg (3 mol %) of CuI, and 27 mg (3 mol %) of $PdCl_2(PPh_3)_2$. The suspension was stirred at rt for 8 h. The reaction mixture was concentrated in vacuo, and the residue was subjected to preparative TLC (2000 μm silica gel GF; 3:1 EtOAc/hexanes) affording 0.15 g (71%) of alcohol **2a** as a tan solid: mp 140 °C dec; ^1H NMR ($CDCl_3$) δ 4.2 (s, 3H), 4.6 (d, J = 4.2 Hz, 2H), 6.9 (d, J = 9.5 Hz, 1H), 7.4 (d, J = 9.4 Hz, 1H). Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.45; H, 4.86; N, 16.81.

3-[3-(6-Fluoropyridazinyl)]-2-propyn-1-ol (2b). A tan solid, 64% yield from **1b**: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (t, J = 6.2 Hz), 4.57 (d, J = 6.2 Hz, 2H), 7.21 (dd, J_{HH} = 9.0 Hz, J_{HF} = 2.0 Hz, 1H), 7.69 (dd, J_{HH} = 9.0 Hz, J_{HF} = 9.3 Hz, 1H). Anal. Calcd for $C_7H_5FN_2O$: C, 55.26; H, 3.31; N, 18.42. Found: C, 54.88; H, 3.23; N, 18.08.

3-[3-[6-(Dimethylamino)pyridazinyl]]-2-propyn-1-ol (2c). A yellow solid, 85% yield from **1c**: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 3.1 (s, 6H), 4.5 (s, 2H), 6.7 (d, J = 9.5 Hz, 1H), 7.2 (d, J = 9.5 Hz, 1H). Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.25; N, 23.72. Found: C, 60.71; H, 6.23; N, 23.37.

***N,N*-Dimethyl-6-(2-phenylethynyl)-3-pyridazinamine (3c).** To a solution of 0.30 g (1.3 mmol) of 3-(dimethylamino)-6-iodopyridazine (**1c**) in 1 mL of DMF was added 0.15 mL (1.4 mmol) of phenylacetylene, 0.35 mL of Et_3N (2.5 mmol), 12 mg (5 mol %) of CuI, and 44 mg (5 mol %) of $PdCl_2(PPh_3)_2$. The suspension was stirred at rt for 8 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL). The organic phase was washed with H_2O (3 × 30 mL), dried, and concentrated in vacuo. The residue obtained was subjected to flash chromatography on silica gel (3:1 hexanes/EtOAc) to yield 0.25 g (85%) as an orange solid: mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 6H), 6.7 (d, J = 9.5 Hz, 1H), 7.4 (m, 4H), 7.6 (m, 2H). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 74.98; H, 5.75; N, 18.51.

3-Methoxy-6-[1-(3-phenoxypropynyl)]pyridazine (4). Prepared as described in the general procedure from **1a** and phenylpropynyl ether as a tan solid, 100% yield: ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 3H), 4.96 (s, 2H), 6.91 (d, J = 9.1 Hz, 1H), 7.03 (m, 3H), 7.32 (m, 2H), 7.40 (d, J = 9.1 Hz, 1H).

3-Methoxy-6-[3-(1-phenoxypropyl)]pyridazine (5). A suspension of propynylpyridazine **4** (1.7 g, 7.1 mmol) and 0.73 g of 5.3% Pd on carbon in 100 mL of EtOAc was hydrogenated at 50 psi in a Paar apparatus for 3 h at which time no further hydrogen uptake was observed. The suspension was filtered through Celite and concentrated in vacuo and the crude material subjected to MPLC (Kieselgel 60; 3:1 hexanes/EtOAc) to provide 1.0 g (58%) of the reduced product **5** as a white solid: mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (dt, J = 8.5, 6.3 Hz, 2H), 3.08 (t, J = 7.4 Hz, 2H), 4.04 (t, J = 6.2 Hz, 2H), 4.10 (s, 3H), 6.87 (d, J = 7.8 Hz, 1H), 6.90 (m, 3H), 7.26 (m, 3H). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.81; H, 6.30; N, 11.45.

General Procedure for the Cross-Coupling of Heteroarylstannanes with 1a, 1c, and 1d. 6-(2-Thienyl)-3-methoxypyridazine (6a). To 0.16 g (0.68 mmol) of 3-methoxy-6-iodopyridazine (**1a**) in 2 mL of DMF was added 0.47 g (1 mmol) of 2-(tributylstannyl)thiophene[10] and 30 mg (5 mol %) of $PdCl_2(PPh_3)_2$, and the mixture was heated at 80 °C for 2 h. After being cooled to rt, the reaction was diluted with 25 mL of EtOAc and washed with H_2O (3 × 25 mL). The organic phase was dried and concentrated in vacuo. Preparative TLC (2000 μm silica gel GF; 3:1 hexane/EtOAc) yielded 0.12 g (93%) of the desired product as a yellow solid: mp 73–74 °C; ^{1}H NMR ($CDCl_3$) δ 4.1 (s, 3H), 7.0 (d, J = 9.2 Hz, 1H), 7.1 (m, 1H), 7.4 (d, J = 7.5 Hz, 1H), 7.5 (d, J = 3.7 Hz, 1H), 7.7 (d, J = 9.2 Hz, 1H). Anal. Calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.17; H, 4.44; N, 14.09.

***N,N*-Dimethyl-6-(2-thienyl)-3-pyridazinamine (6c).** A white solid in 77% yield: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 6H), 6.7 (d, J = 9.6 Hz, 1H), 7.1 (m, 1H), 7.3 (d, J = 2.6 Hz, 1H), 7.4 (d, J = 1.9 Hz, 1H), 7.5 (d, J = 9.5 Hz, 1H). Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47. Found: C, 58.12; H, 5.33; N, 20.07.

3-(Methylthio)-6-(2-thienyl)pyridazine (6d): 75% yield; mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 2.7 (s, 3H), 7.1 (t, J = 3.8 Hz, 1H), 7.3 (d, J = 9.0 Hz, 1H), 7.4 (d, J = 5.0 Hz, 1H), 7.5 (d, J = 9.0 Hz, 1H), 7.8 (d, J = 3.6 Hz, 1H). Anal. Calcd for $C_9H_8N_2S_2$: C, 51.89; H, 3.87; N, 13.45. Found: C, 51.77; H, 3.78; N, 13.02.

3-Methoxy-6-[5-[2-(1,3-dioxolanyl)]furanyl]pyridazine (7a). A mixture (0.20 g, 0.80 mmol) of 3-methoxy-6-iodopyrazine (**1a**), 2 mL of THF, 0.36 g (1.2 mmol) of 2-[2-[5-(trimethylstannyl)furanyl]]-1,3-dioxolane[11] and 28 mg (4 mol %) of $PdCl_2(PPh_3)_2$ was heated to reflux for 8 h. After being cooled to rt, the reaction was diluted with EtOAc (25 mL) and washed with H_2O (3 × 25 mL). The organic phase was dried and concentrated in vacuo. Preparative TLC (2000 μm silica gel GF; EtOAc) yielded 0.21 g (81%) of **7a** as a yellow solid: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 4.0 (m, 2H), 4.1 (m, 2H), 4.1 (s, 3H), 6.0 (s, 1H), 6.6 (d, J = 3.4 Hz, 1H), 7.0 (d, J = 9.3 Hz, 1H), 7.1 (d, J = 3.4 Hz, 1H), 7.9 (d, J = 9.3 Hz, 1H). Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.82; N, 11.29. Found: C, 57.71; H, 4.82; N, 10.89.

***N,N*-Dimethyl-6-[5-[2-(1,3-dioxolanyl)furanyl]-3-pyridazinamine (7c).** A brown solid in 85% yield: mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 3.1 (s, 6H), 4.0 (m, 2H), 4.1 (m, 2H), 6.0 (s, 1H), 6.5 (d, J = 3.4 Hz, 1H), 6.7 (d, J = 9.5 Hz, 1H), 7.0 (d, J = 3.3 Hz, 1H), 7.6 (d, J = 9.6 Hz, 1H). Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 60.08; H, 5.72; N, 15.78.

General Procedure for the Suzuki Cross-Coupling with 1a and 1c. 3-Methoxy-6-phenylpyridazine (8a). A mixture of 0.20 g (0.85 mmol) of 3-methoxy-6-iodopyridazine (**1a**), 5 mL of toluene, 0.12 g (1.0 mmol) of phenylboronic acid, 0.9 mL (1.8 mmol) of 2 M Na_2CO_3, and 30 mg (3 mol %) of $Pd(PPh_3)_4$ was heated to reflux for 12 h. The reaction was allowed to cool to rt and then concentrated in vacuo. The residue was diluted with H_2O (20 mL) and then extracted with EtOAc (30 mL). The organic layer was washed with H_2O (3 × 30 mL), dried, and concentrated in vacuo. The solid was chromatographed on silica gel eluting with 2:1 hexane/EtOAc to yield 0.13 g (76%) of **8a** as a white solid: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 4.2 (s, 3H), 7.0 (d, J = 9.5 Hz, 1H), 7.5 (m, 3H), 7.8 (d, J = 9.4 Hz, 1H), 8.0 (d, J = 7.3 Hz, 2H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.68; H, 5.33; N, 14.89.

***N,N*-Dimethyl-6-phenyl-3-pyridazinamine (8c).** A pale yellow solid, 58% yield: mp 115–116 °C; ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 6H), 6.9 (d, J = 9.5 Hz, 1H), 7.4 (m, 3H), 7.6 (d, J = 9.5 Hz, 1H), 8.0 (d, J = 7.4 Hz, 2H). Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 71.91; H, 6.56; N, 20.88.

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