SYNTHESIS AND REACTION OF TRIBUTYLSTANNYLPYRAZOLES

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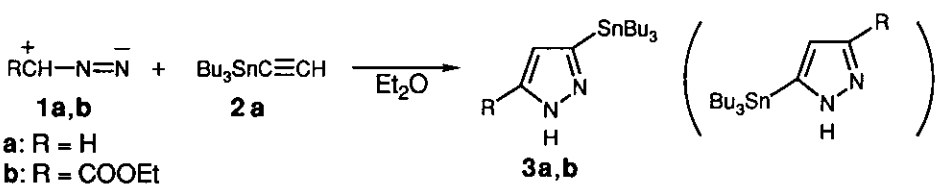
Abstract—1,3-Dipolar cycloaddition reaction of diazomethane and ethyl diazoacetate with tributylstannylacetylenes occurred regioselectively to afford the corresponding 3(5)-tributylstannylpyrazoles. The cycloaddition reaction of 3-phenylsydnone with the stannylacetylenes proceeded also regioselectively, and 3-tributylstannyl-1-phenylpyrazoles were isolated. 4-Tributylstannyl- and 5-tributylstannyl-1-phenylpyrazole were prepared by the stannylation of 4-lithio- and 5-lithio-1-phenylpyrazoles with tributylstannyl chloride. Iodination, benzoylation, and phenylation of the stannylpyrazoles were examined.

Previously, we reported that the 1,3-dipolar cycloaddition reaction of nitrile oxides with tributylstannylacetylene gave 5-tributylstannylisoxazoles which are utilized for the synthesis of 5-substituted isoxazole derivatives.[1] Our next interest was focused on the synthesis of tributylstannylpyrazoles, because tributylstannyl groups on heteroaromatic rings were realized to be useful for introducing regioselectively various substituents into the rings. In the present paper, we report the synthesis of the 3-tributylstannylpyrazoles by the 1,3-dipolar cycloaddition reaction of di-azomethane, ethyl diazoacetate, and 3-phenylsydnone with tributylstannylacetylenes together with the synthesis of 4- and 5-tributylstannylpyrazoles by the stannylation of 1-phenylpyrazoles *via* 4- and 5-lithiopyrazoles. Some chemical reactions of the stannylpyrazoles thus obtained are also described.

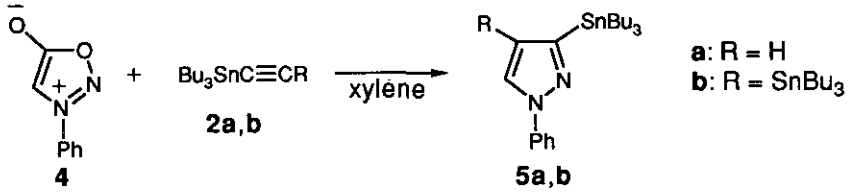
When an ethereal solution of tributylstannylacetylene (**2 a**) and excess diazomethane (**1 a**) was allowed to stand for 5 days, regioselective cycloaddition product, 3(5)-tributylstannylpyrazole (**3 a**), was obtained as a sole product. Similarly, the reaction of **2 a** with ethyl diazoacetate gave ethyl 3(5)-tributylstannyl-5(3)-pyrazolecarboxylate (**3 b**).



Scheme 1

On the other hand, the 1,3-dipolar cycloaddition reaction of 3-phenylsydnone (**4**)[2] with **2 a** in boiling xylene gave

3-tributylstannyl-1-phenylpyrazole (**5a**) in 85% yield. The reaction of **4** with bis(tributylstannyl)acetylene (**2b**) *under similar conditions quantitatively proceeded* to give 3,4-bis(tributylstannyl)pyrazole (**5b**).



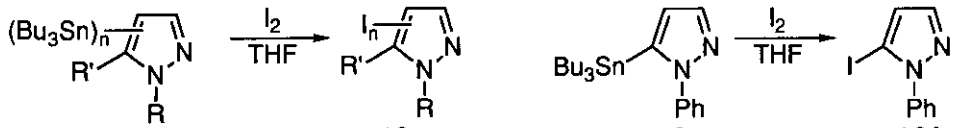
Scheme 2

In order to synthesize 4- and 5-stannylpyrazoles, the stannylation *via* the corresponding lithiopyrazoles was examined. The lithiation of 4-bromo-1-phenylpyrazole (**6**)[3] with butyllithium followed by metal exchange reaction of the resultant lithio compound with tributylstannyl chloride yielded 4-tributylstannyl-1-phenylpyrazole (**7**). 5-Tributylstannyl-1-phenylpyrazole (**9**), *a positional isomer of* **7**, *was easily prepared via direct lithiation of* 1-phenylpyrazole (**8**).

Scheme 3

Since the preparation of 3-, 4-, and 5-tributylstannylpyrazoles was accomplished, some reactions of the tributylstannylpyrazoles were investigated. The iodination of the tributylstannylpyrazoles (**3**, **5**, **7**, and **9**) with iodine in THF proceeded smoothly at any position to give satisfactory results shown in Table I.

Table I. Iodination of Tributylstannylpyrazoles

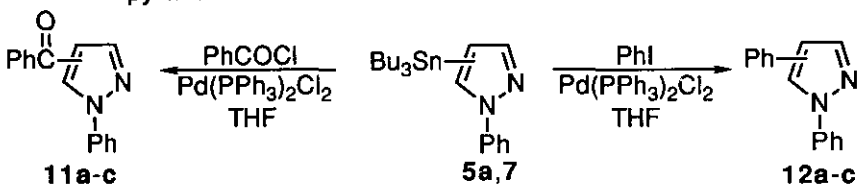


Product No.	n	Position	R	R'	Reaction time	Yield (%)	mp (°C) or bp (°C)/mmHg
10a	1	3	H	H	2 h	63	72-73
10b	1	3	H	COOEt	2 h	52	104-106
10c	1	3	Ph	H	1 h	94	180/5
10d	2	3,4	Ph	H	20 min	68	77-79
10e	1	4	Ph	H	20 min	59	82-84
10f					20 min	61	94-96

Next, the palladium-catalyzed benzoylation and phenylation of tributylstannyl-1-phenylpyrazoles (**5a**, **7**, and **9**) with benzoyl chloride and iodobenzene using dichlorobis(triphenylphosphine)palladium as a catalyst was exam-

ined. The palladium-catalyzed reactions of 3- (**5a**) and 4-tributylstannyl-1-phenylpyrazole (**7**) yielded the expected products (**11a, b** and **12a,b**) in 42-59% yields, but differently from the iodination, the reactions of the 5-tributylstannylpyrazole (**9**) did not give the expected products (**11c** and **12c**).

Tables II and III. Palladium-Catalyzed Benzoylation and Phenylation of Tributylstannylpyrazoles



11a-c **5a,7** **12a-c**

Product No.	Position	Reaction time	Yield (%)	mp (°C) or bp (°C)/mmHg
11a	3	3 days	54	220/6
11b	4	3 h	42	123-125
11c	5	20 h	0	—

Product No.	Position	Reaction time	Yield (%)	mp (°C)
12a	3	20 h	59	81-83
12b	4	24 h	49	95-97
12c	5	24 h	0	—

It is well known that the electrophilic substitution such as halogenation[3] and Friedel-Crafts type acylation[4] of pyrazoles occur at the 4-position. Accordingly, 3(5)-tributylstannylpyrazoles synthesized by the 1,3-dipolar cycloaddition reaction with tributylstannylacetylenes can be key compounds to introduce a substituent at the 3-position of pyrazole ring.

EXPERIMENTAL

3(5)-Tributylstannylpyrazole (3a)

To an ethereal (20 ml) solution of diazomethane (**1a**) (*ca.* 15 mmol) prepared from nitrosomethylurea (2.6 g, 25 mmol), tributylstannylacetylene (**2a**) (1.26 g, 4 mmol) was added, and the mixture was stirred at room temperature for 5 days until the yellow color of the mixture disappeared. After evaporation of the solvent, the residue was chromatographed on a silica gel column with $CHCl_3$ as an eluent to give a viscous liquid (1.08 g, 75%). ^{1}H-Nmr ($CDCl_3$, ppm): 0.7-1.8 (27H, m), 6.48 (1H, d, J=2 Hz), 7.70 (1H, d, J=2 Hz), 10.3-11.8 (1H, br s). High Resolution ms Calcd for $C_{11}H_{21}N_2Sn$ (M^+-C_4H_9): 301.0727. Found: 301.0721.

Ethyl 3(5)-Tributylstannylpyrazole-5(3)-carboxylate (3b)

A mixture of ethyl diazoacetate (**1b**) (0.35 g, 3 mmol) and **2a** (0.63 g, 2 mmol) was stirred at room temperature for 5 days. The reaction mixture was chromatographed on a silica gel column with hexane-AcOEt (2:1) as an eluent to give a viscous liquid (0.46 g, 53%). ^{1}H-Nmr ($CDCl_3$, ppm): 0.6-1.8 (30H, m), 4.36 (2H, d, J=7 Hz), 6.86 (1H, s). High Resolution ms Calcd for $C_{14}H_{25}N_2O_2Sn$ (M^+-C_4H_9): 373.0938. Found: 373.0927.

3-Tributylstannyl-1-phenylpyrazole (5a)

A mixture of 3-phenylsydnone (**4**) (0.81 g, 5 mmol) and **2a** (2.36 g, 7.5 mmol) in xylene (5 ml) was refluxed for 6 h. After cooling, the mixture was diluted with C_6H_6 and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-C_6H_6 (5:1) as an eluent. The product obtained from the eluate was distilled under reduced pressure to give a colorless liquid (1.83 g, 85%), bp 190°C/0.6 mmHg (bath temp.). ^{1}H-Nmr ($CDCl_3$, ppm): 0.7-1.9 (27H, m), 6.52 (1H, d, *J*=2 Hz), 7.1-7.9 (5H, m), 7.96 (1H, d, *J*=2 Hz). *Anal.* Calcd for $C_{20}H_{34}N_2Sn$: C, 58.24; H, 7.86; N, 6.47. Found: C, 58.15; H, 7.86; N, 6.59.

3,4-Bis(tributylstannyl)-1-phenylpyrazole (5b)

A mixture of **4** (0.81 g, 5 mmol), bis(tributylstannyl)acetylene (**2b**) (4.54 g, 7.5 mmol) in xylene (5 ml) was refluxed for 16 h. After evaporation of the solvent, the residue was diluted with water and extracted with Et_2O. The ethereal extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on an alumina column with hexane-Et_3N (9:1) as an eluent to give a viscous oil (3.56 g, 98%). ^{1}H-Nmr ($CDCl_3$, ppm): 0.6-1.9 (54H, m), 7.1-7.9 (6H, m). ms (*m/z*): 547 (M^+-C_4H_9).[5]

4-Tributylstannyl-1-phenylpyrazole (7)

1.56M Butyllithium in hexane (9.46 ml, 22 mmol) was added dropwise to a solution of 4-bromo-1-phenylpyrazole (**6**) (4.48 g, 20 mmol) in Et_2O (60 ml) with stirring under nitrogen atmosphere below -60°C. The resulting suspension was allowed to warm at -20~-10°C, and stirred at the same temperature for 6 h. Then, tributylstannyl chloride (7.16 g, 22 mmol) in Et_2O (50 ml) was added at such rate as to keep the reaction temperature below 0°C. The mixture was allowed to warm to room temperature and stirred overnight. After addition of water, the ethereal solution was separated, and the aqueous phase was extracted with Et_2O. The residue obtained from the combined ethereal layer was distilled under reduced pressure to give a colorless liquid (7.73 g, 89%), bp 176°C/0.3 mmHg. ^{1}H-Nmr ($CDCl_3$, ppm): 0.7-1.8 (27H, m), 7.2-7.9 (7H, m). High Resolution ms Calcd for $C_{17}H_{25}N_2Sn$ (M^+-C_4H_9): 377.1040. Found: 377.1051.

5-Tributylstannyl-1-phenylpyrazole (9)

1.56 M Butyllithium in hexane (8.60 ml, 20 mmol) was added dropwise to a solution of 1-phenylpyrazole (**8**) (2.88 g, 20 mmol) in Et_2O (60 ml) with stirring under nitrogen atmosphere at -10~0°C. After stirring of the suspension at the same temperature for 1 h, tributylstannyl chloride (7.16 g, 22 mmol) in Et_2O (50 ml) was added at such rate as to keep the reaction temperature below 0°C. The mixture was allowed to warm to room temperature and stirred for 2 h. After addition of water, the ethereal solution was separated, and the aqueous phase was extracted with Et_2O. The residue obtained from the combined ethereal layer was distilled under reduced pressure to give a colorless liquid (6.89 g, 80%), bp 164°C/0.5 mmHg. ^{1}H-Nmr ($CDCl_3$, ppm): 0.7-1.7 (27H, m), 6.35 (1H, d, *J*=2 Hz), 7.2-7.9 (6H, m).

Anal. Calcd for $C_{20}H_{34}N_2Sn$: C, 58.24; H, 7.86; N, 6.47. Found: C, 58.31; H, 7.72; N, 6.49.

General Procedure for the Reaction of Stannylpyrazoles with Iodine

Iodine (0.50 g, 2 mmol) in THF (15 ml) was added dropwise to a pyrazole (2 mmol) in THF (15 ml) with stirring at room temperature, and the mixture was stirred for the time shown in Table I. After addition of water, the mixture was extracted with Et_2O. The ethereal extract was washed with aq. $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column or distilled to give the iodopyrazole.

3(5)-Iodopyrazole (10a)

^{1}H-Nmr ($CDCl_3$, ppm): 6.47 (1H, d, *J*=2 Hz), 7.36 (1H, d, *J*=2 Hz), 12.1-13.0 (1H, brs). Lit.,[6] mp 72-73°C.

Ethyl 3(5)-Iodolpyrazole-5(3)-carboxylate (10b)

^{1}H-Nmr ($CDCl_3$, ppm):1.36 (3H, t, *J*=7 Hz), 4.43 (2H, q, *J*=7 Hz), 6.96 (1H, s), 9.7-12.9 (1H, br s). *Anal.* Calcd for $C_6H_7N_2O_2I$: C, 27.07; H, 2.63; N, 10.53. Found: C, 27.09; H, 2.61; N, 10.51.

3-Iodo-1-phenylpyrazole (10c)

^{1}H-Nmr ($CDCl_3$, ppm): 6.56 (1H, d, *J*=2 Hz), 7.2-7.7 (6H, m). High Resolution ms Calcd for $C_9H_7N_2I$: 269.9654. Found: 269.9623.

3,4-Diiodo-1-phenylpyrazole (10d)

^{1}H-Nmr ($CDCl_3$, ppm): 7.2-7.7 (5H, m), 7.77 (1H, s). *Anal.* Calcd for $C_9H_6N_2I_2$: C, 27.30; H, 1.53; N, 7.01. Found: C, 27.18; H, 1.55; N, 7.04.

4-Iodo-1-phenylpyrazole (10e)

^{1}H-Nmr ($CDCl_3$, ppm): 7.3-7.7 (6H, m), 7.95 (1H, s). Lit.,[7] mp 82-84°C.

5-Iodo-1-phenylpyrazole (10f)

^{1}H-Nmr ($CDCl_3$, ppm): 6.63 (1H, d, *J*=2 Hz), 7.50 (5H, s), 7.68 (1H, d, *J*=2 Hz). *Anal.* Calcd for $C_9H_7N_2I$: C, 40.03; H, 2.61; N, 10.37. Found: C, 39.85; H, 2.47; N, 10.28.

General Procedure for the Palladium-Catalyzed Reaction of Stannylpyrazoles with Benzoyl Chloride

A mixture of a stannylpyrazole (2 mmol), benzoyl chloride (0.28 g, 2 mmol), and $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) in THF (15 ml) was refluxed for the time shown in Table II. After addition of 0.5 M KF aq. solution, the mixture was extracted with Et_2O. The ethereal extract was dried over $MgSO_4$, and the extract was concentrated under reduced pressure. The residue was chromatographed on a silica gel column or distilled to give the phenyl pyrazolyl ketone.

Phenyl 3-(1-Phenylpyrazolyl) Ketone (11a)

^{1}H-Nmr ($CDCl_3$, ppm): 7.03 (1H, d, *J*=2 Hz), 7.1-7.8 (8H, m), 7.90 (1H, d, *J*=2 Hz), 8.3-8.6 (2H, m). *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 10.68. Found: C, 77.68; H, 5.13; N, 10.98.

Phenyl 4-(1-Phenylpyrazolyl) Ketone (11b)

^{1}H-Nmr ($CDCl_3$, ppm): 7.3-8.0 (10H, m), 8.15 (1H, s), 8.45 (1H, s). Lit.,[8] mp 125-125.5°C.

General Procedure for the Palladium-Catalyzed Reaction of Stannylpyrazoles with Iodobenzene

A mixture of a stannylpyrazole (2 mmol), iodobenzene (40 mg, 2 mmol), and $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) in THF (15 ml) was refluxed for the time shown in Table III. After addition of 0.5 M KF aq. solution, the mixture was extracted with Et_2O. The ethereal extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column and recrystallized to give the phenylpyrazole.

1,3-Diphenylpyrazole (12a)

^{1}H-Nmr ($CDCl_3$, ppm): 6.63 (1H, d, *J*=2 Hz), 7.1-8.0 (11H, m). Lit.,[9] mp 84-85°C.

1,4-Diphenylpyrazole (12b)

^{1}H-Nmr ($CDCl_3$, ppm): 7.2-7.9 (10H, m), 7.96 (1H, s), 8.12 (1H, s). Lit.,[10] mp 97-98°C.

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