SYNTHESIS AND REACTION OF TRIBUTYLSTANNYLPYRAZoles

Takao Sakamoto, Futoshi Shiga, Daishi Uchiyama, Yoshinori Kondo, and Hiroshi Yamanaka*

Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan

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-phenylsydnones 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 stannyipyrazoles were examined.

Previously, we reported that the 1,3-dipolar cycloaddition reaction of nitrile oxides with tributylstannylicetylene gave 5-tributylstannylisoxazoles which are utilized for the synthesis of 5-substituted isoxazole derivatives.1 Our next interest was focused on the synthesis of tributylstannyipyrazoles, 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-tributylstannyipyrazoles by the 1,3-dipolar cycloaddition reaction of diazomethane, ethyl diazoacetate, and 3-phenylsydnones with tributylstannylicetylenes together with the synthesis of 4- and 5-tributylstannyipyrazoles by the stannylation of 1-phenylpyrazoles via 4- and 5-lithiopyrazoles. Some chemical reactions of the stannyipyrazoles thus obtained are also described.

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

On the other hand, the 1,3-dipolar cycloaddition reaction of 3-phenylsydnones (4)2 with 2a in boiling xylene gave
3-tributylstannyl-1-phenylpyrazole (5a) in 85% yield. The reaction of 4 with bis(tributylstanny)acetylene (2b) under similar conditions quantitatively proceeded to give 3,4-bis(tributylstannyl)pyrazole (5b).

\[ \text{Scheme 2} \]

In order to synthesize 4- and 5-stannylpyrazoles, the stannylation via the corresponding lithiumpyrazoles 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).

\[ \text{Scheme 3} \]

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**

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

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Position</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
<th>mp (°C) or bp (°C)/mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>3</td>
<td>3 days</td>
<td>54</td>
<td>220/6</td>
</tr>
<tr>
<td>11b</td>
<td>4</td>
<td>3 h</td>
<td>42</td>
<td>123-125</td>
</tr>
<tr>
<td>11c</td>
<td>5</td>
<td>20 h</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

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\(_2\)Sn (M\(^+\)-C\(_4\)H\(_3\)): 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\(_2\)O\(_2\)Sn (M\(^+\)-C\(_4\)H\(_3\)): 373.0938. Found: 373.0927.
3-Trbutylstannyl-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 C6H6 and washed with water. The organic layer was dried over MgSO4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane-C6H6 (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.). 1H-Nmr (CDCl3, 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 C20H14N2Sn: C, 58.24; H, 7.86; N, 6.47. Found: C, 58.15; H, 7.86; N, 6.59.

3,4-Bis(trbutylstannyl)-1-phenylpyrazole (5b)
A mixture of 4 (0.81 g, 5 mmol), bis(tributylstannyi)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 Et2O. The ethereal extract was dried over MgSO4 and concentrated under reduced pressure. The residue was chromatographed on an alumina column with hexane-Et3N (9:1) as an eluent to give a viscous oil (3.56 g, 98%). 1H-Nmr (CDCl3, ppm): 0.6-1.9 (54H, m), 7.1-7.9 (6H, m). ms (m/z): 547 (M+H).5

4-Trbutylstannyl-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 Et2O (60 ml) with stirring under nitrogen atmosphere below -60°C. The resulting suspension was allowed to warm to -20 to -10°C, and stirred at the same temperature for 6 h. Then, tributylstannyl chloride (7.16 g, 22 mmol) in Et2O (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 Et2O. 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. 1H-Nmr (CDCl3, ppm): 0.7-1.8 (27H, m), 7.2-7.9 (7H, m). High Resolution ms Calcd for C17H25N2Sn (M+H): 377.1040. Found: 377.1051.

5-Trbutylstannyl-1-phenylpyrazole (8)
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 Et2O (60 ml) with stirring under nitrogen atmosphere at -10 to 0°C. After stirring of the suspension at the same temperature for 1 h, tributylstannyl chloride (7.16 g, 22 mmol) in Et2O (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 Et2O. 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. 1H-Nmr (CDCl3, ppm): 0.7-1.7 (27H, m), 6.35 (1H, d, J=2 Hz), 7.2-7.9 (6H, m).

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 Et₂O. The ethereal extract was washed with aq. Na₂S₂O₃, dried over MgSO₄, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column or distilled to give the iodopyrazole.

3(5)-Iodopyrazole (10a)

1H-Nmr (CDCl₃, ppm): 6.47 (1H, d, J=2 Hz), 7.36 (1H, d, J=2 Hz), 12.1-13.0 (1H, brs). mp 72-73°C.

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

1H-Nmr (CDCl₃, 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 C₆H₇N₂O₂: C, 27.07; H, 2.63; N, 10.53. Found: C, 27.09; H, 2.61; N, 10.51.

3-Iodo-1-phenylpyrazole (10c)

1H-Nmr (CDCl₃, ppm): 6.56 (1H, d, J=2 Hz), 7.2-7.7 (6H, m). High Resolution ms Calcd for C₁₉H₁₇N₂: 269.9654. Found: 269.9623.

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

1H-Nmr (CDCl₃, ppm): 7.2-7.7 (5H, m), 7.77 (1H, s). Anal. Calcd for C₁₉H₁₆N₂: C, 27.30; H, 1.53; N, 7.01. Found: C, 27.18; H, 1.55; N, 7.04.

4-Iodo-1-phenylpyrazole (10e)

1H-Nmr (CDCl₃, ppm): 7.3-7.7 (6H, m), 7.95 (1H, s). Lit., 7 mp 82-84°C.

5-Iodo-1-phenylpyrazole (10f)

1H-Nmr (CDCl₃, ppm): 6.63 (1H, d, J=2 Hz), 7.50 (5H, s), 7.68 (1H, d, J=2 Hz). Anal. Calcd for C₁₉H₁₇N₂: 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(PPh₃)₂Cl₂ (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 Et₂O. The ethereal extract was dried over MgSO₄, 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)

1H-Nmr (CDCl₃, 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 C₁₆H₁₂N₂O: C, 77.40; H, 4.87; N, 10.88. 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$_3$)$_2$Cl$_2$ (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$_2$O. 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.

REFERENCES


5. Since there are 100 stable isotopes in compound (5b) which contains two tin atoms, measurement of the high resolution mass spectrum of 5b is difficult.


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