LOW-VALENT TITANIUM INDUCED REDUCTIVE CYCLIZATION OF ISOTHIOCYANATES TO INDOLE DERIVATIVES

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Abstract - Reductive cyclization of aryl isothiocyanates (1) induced by titanium tetrachloride - zinc provides a synthesis of substituted indol-2-carbothioamides (2).

The reductive coupling of carbonyl compounds with low-valent titanium reagents constitutes an attractive route to alkenes, which has found considerable application in synthesis. In fact, many other functional groups can also undergo coupling reactions under these conditions. For example, the reductive cyclization of nitriles to symmetrically substituted tetraalkylpyrazines and the reductive coupling of phenyl isocyanate to afford substituted urea and biurea. Herein, we present our preliminary results on the synthesis of substituted indole-2-carbothioamides (2) using a reductive cyclization of isothiocyanates by TiCl₄-Zn.

![Chemical structure](image)

Table 1. Preparation of 2

<table>
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<tr>
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<th>R (1)</th>
<th>2</th>
<th>R (2)</th>
<th>R' (2)</th>
<th>Yield(%)</th>
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<td>H</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>44</td>
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<tr>
<td>1b</td>
<td>2-CH₃</td>
<td>2b</td>
<td>2-CH₃</td>
<td>7-CH₃</td>
<td>11</td>
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<tr>
<td>1c</td>
<td>4-CH₃</td>
<td>2c</td>
<td>4-CH₃</td>
<td>5-CH₃</td>
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<tr>
<td>1d</td>
<td>4-Cl</td>
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<tr>
<td>1e</td>
<td>3-CH₃O</td>
<td>2e</td>
<td>3-CH₃O</td>
<td>6-CH₃O</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2e'</td>
<td>3-CH₃O</td>
<td>4-CH₃O</td>
<td>7</td>
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</table>

Isothiocyanates (1a-e) were easily prepared from the corresponding amines following a known procedure. As shown above, reductive cyclizations of isothiocyanates (1a-e) with TiCl₄-Zn in the presence of THF afforded 3-arylamino-1H-indole-2-(N-aryl)carbothioamides (2a-f).
The formation of the indoles was confirmed unambiguously by a single crystal X-Ray analysis of 2a, and the result of X-Ray crystallographic analysis is depicted in Figure 1.

Figure 1. X-Ray crystal structure of 2a

The mechanism of the reaction may be postulated as Scheme 1.

Isothiocyanates (1) are reductivity dimerized with an initial formation of vicinal dithiimidate intermediates (3). The desulfurization of the intermediate (3) gives a radical which attacks the aromatic ring and captures one hydrogen from the molecule of THF to form the indole ring (4). The desulfurization of indole compound (4) gives another radical which attacks a third isothiocyanate molecule and captures one hydrogen from solvent molecule to form a thioanilide.

In hope of optimized the yield of this reaction, we performed the reaction in the absence of solvent. However, we found N,N-diphenylthiourea, the two molecular coupling product, rather than the expected substituted indole-2-carbothioamides(2a), was achieved in high yield (91%).
In conclusion, our work extended the field of low-valent titanium and provided, in certain cases, an attractive one-step method to synthesis some indole derivatives.

**EXPERIMENTAL**

Melting points are uncorrected. IR spectra were measured on a DS-408 spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra were recorded by FT-90Q spectrometer using TMS as an internal standard. MS spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed with a 240-C instrument.

General procedure for generation of 2. A dry 100 mL flask was charged with zinc dust (5.2 g, 80 mmol), THF (50 mL) and TiCl$_4$ (4.4 mL, 40 mmol). The mixture was refluxed for 2 h under an atmosphere of argon, then a solution of 1a (3.75 g, 30 mmol) in THF (15 mL) was slowly added. The reaction mixture was stirred for 20 h at rt. After removing the THF, the mixture was quenched with 15% K$_2$CO$_3$ solution and extracted with CHCl$_3$. The combined organic layer was washed with water, dried over Na$_2$SO$_4$ and evaporated. The residue was subject to chromatography separation on silica gel (300-400 mesh) with petroleum ether (bp 60-90°C)-ethyl acetate (4:1) as eluents. The red crude product washed with ether and recrystallized from benzene, yellow needles crystal was obtained (1.51 g, 44%). The procedures of other derivatives are similar to above.

3-Phenylamino-1H-indole-2-(N-3-methoxyphenyl)carbothioamides (2a): mp 190-192°C; IR (KBr) cm$^{-1}$: 3300, 3250-3150, 1590, 1560, 1520, 1490; $^1$H-NMR (90 MHz, CDCl$_3$): $\delta$=5.40(s, 3H, NH), 6.74-7.73(m, 14H, ArH), 9.50(s, 1H, NH), 12.04(s, 1H, NHCS). $^{13}$C-NMR (CDCl$_3$): $\delta$=112.3, 115.7, 120.2, 121.3, 122.7, 125.6, 126.2, 128.3, 128.8, 129.7, 130.3, 135.1, 138.9, 145.6, 183.8. MS(EI): 343(M$^+$), 310, 250, 218, 135. Anal. Caled for C$_{29}$H$_{25}$N$_2$S: C 73.44, H 5.09, N 12.41. Found: C 73.94, H 5.09, N 12.41.

3-(2-Methylphenylamino)-7-methyl-1H-indole-2-(N-2-methylphenyl)carbothioamides (2b): mp 160-162°C; IR (KBr) cm$^{-1}$: 3350, 3250-3150, 1600, 1580, 1545, 1495; $^1$H-NMR (90 MHz, CDCl$_3$): $\delta$=2.09(s, 3H, CH$_3$), 2.43(s, 3H, CH$_3$), 2.55(s, 3H, CH$_3$), 6.57-7.44(m, 11H, ArH), 7.77(s, 1H, NH), 9.52(s, 1H, NH), 11.49(s, 1H, NHCS). $^{13}$C-NMR (CDCl$_3$): $\delta$=111.7, 16.3, 108.3, 115.5, 121.0, 121.6, 124.6, 125.1, 126.2, 126.3, 127.3, 130.8, 133.4, 144.2, 173.8. MS(EI): 385(M$^+$), 352, 278, 149. Anal. Caled for C$_{28}$H$_{25}$N$_2$S: C 74.77, H 6.01, N 10.90. Found: C 75.05, H 6.16, N 10.73.

3-(4-Chlorophenylamino)-5-methyl-1H-indole-2-(N-4-chlorophenyl)carbothioamides (2c): mp 190-192°C; IR (KBr) cm$^{-1}$: 3350, 3250-3150, 1600, 1595, 1545, 1525, 1500; $^1$H-NMR (90 MHz, CDCl$_3$): $\delta$=2.25(s, 3H, CH$_3$), 2.30(s, 3H, CH$_3$), 3.32(s, 3H, CH$_3$), 5.27(s, 1H, NH), 6.65-7.62(m, 11H, ArH), 9.44(s, 1H, NH), 12.08(s, 1H, NHCS). $^{13}$C-NMR (CDCl$_3$): $\delta$=20.05, 21.0, 21.4, 112.0, 115.7, 119.3, 122.8, 126.1, 127.6, 128.4, 129.3, 130.2, 130.3, 130.5, 130.6, 133.8, 136.0, 136.7, 143.4, 183.6. MS(EI): 385(M$^+$), 352, 278, 245, 149. Anal. Caled for C$_{28}$H$_{23}$Cl$_2$N$_2$S: C 74.77, H 6.01, N 10.90. Found: C 75.23, H 6.16, N 10.99.

3-(3-Methoxyphenylamino)-6-methoxy-1H-indole-2-(N-3-methoxyphenyl)carbothioamides (2e): mp 177-179°C; IR (KBr) cm$^{-1}$: 3300, 3250-3150, 1620, 1600, 1560, 1520, 1490; $^1$H-NMR (90 MHz, CDCl$_3$): $\delta$=3.68(s, 3H, OCH$_3$), 3.73(s, 3H, OCH$_3$), 3.80(s, 3H, OCH$_3$), 5.49(s, 1H, NH), 6.32-7.54(m, 11H, ArH), 9.34(s, 1H, NH), 11.79(s, 1H, NHCS). $^{13}$C-NMR (CDCl$_3$): $\delta$=55.2, 55.3, 55.5, 94.2, 102.0, 106.6, 107.9, 108.3, 112.2, 112.5, 112.6, 114.7, 116.3, 120.0, 121.1, 129.4, 130.5, 136.5, 140.2, 147.0,

3-(3-Methoxyphenylamino)-4-methoxy-1H-indole-2-(N-3-methoxyphenyl)carbothioamides (2e*): mp 167-168°C; IR(KBr) cm⁻¹: 3330, 3150, 1600, 1550, 1520, 1480; 'H-NMR (90 MHz, CDCl₃): δ = 3.68(s, 3H, OCH₃), 3.71(s, 3H, OCH₃), 3.74(s, 3H, OCH₃), 5.97(s, 1H, NH), 6.34-7.44(m, 1H, ArH), 9.46(s, 1H, NH), 11.64(s, 1H, NHCS). 'C-NMR (CDCl₃): δ = 55.2, 55.3, 55.4, 100.3, 102.2, 105.1, 106.7, 108.0, 108.6, 112.3, 115.0, 116.9, 126.7, 128.4, 129.3, 130.2, 136.6, 140.1, 147.3, 155.6, 158.3, 159.8, 161.0, 183.1. MS(EI): 433(M*), 400, 310, 268, 165, 122. Anal. Calcd for C₆₆H₅₉N₉O₃S: C 66.49, H 5.35, N 9.70. Found: C 66.55, H 5.35, N 9.70.

General Procedure for Compound (3a).- To a dry 100mL flask charged with I (15 mmol) and zinc dust (2.60 g, 40 mmol), was added 2.2 mL (20 mmol) TiCl₄ dropwise via a syringe at 80°C under an argon atmosphere. When the addition was complete, the mixture was heated to 100°C for 2 h. After cooling to rt, the solid mixture was hydrolyzed with 5% aqueous HCl solution and extracted with CHCl₃ (50 mL×3). The combined CHCl₃ extract was washed with water (30 mL×3), dried over anhydrous Na₂SO₄, and the solvent was removed in vacuo. The crude product was recrystallized with ethanol and yellow plate crystal was obtained (3.10 g, 91%, mp 154-156°C lit., 8 154°C).

ACKNOWLEDGMENT
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REFERENCES AND NOTES
5. Yellow plate single crystals suitable for X-Ray diffraction analysis were obtained from ethyl acetate-petroleum ether(60-90°C): Space group P2₁/c, a=13.991(1), b=5.748(1), c=21.569Å; β=90.619(8), Z=4.1619 reflection obtained, R=0.034, Rω=0.040. Further details of the crystal structure investigation of 2a may be obtained from the Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England, on quoting the depository number: CFI1106.
6. All the peaks of the labile protons disappeared after the addition of the D₂O.
7. As there was a little of H₂O in the system, the peaks of the labile protons did not appear.

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