

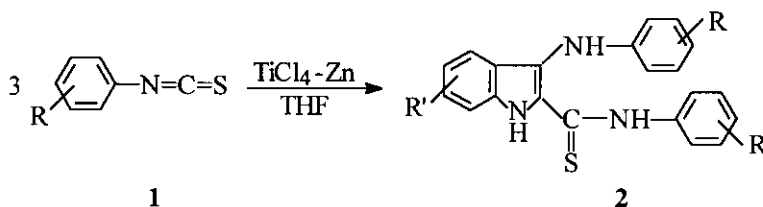
## LOW-VALENT TITANIUM INDUCED REDUCTIVE CYCLIZATION OF ISOTHIOCYANATES TO INDOLE DERIVATIVES

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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**).

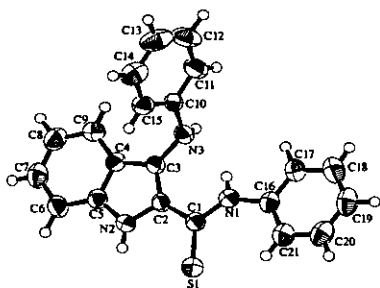
The reductive coupling of carbonyl compounds with low-valent titanium reagents constitutes an attractive route to alkenes, which has found considerable application in synthesis.<sup>1</sup> In fact, many other functional groups can also undergo coupling reactions under these conditions. For example, the reductive cyclization of nitriles to symmetrically substituted tetraalkylpyrazines<sup>2</sup> and the reductive coupling of phenyl isocyanate to afford substituted urea and biurea.<sup>3</sup> Herein, we present our preliminary results on the synthesis of substituted indole-2-carbothioamides (**2**) using a reductive cyclization of isothiocyanates by  $\text{TiCl}_4\text{-Zn}$ .



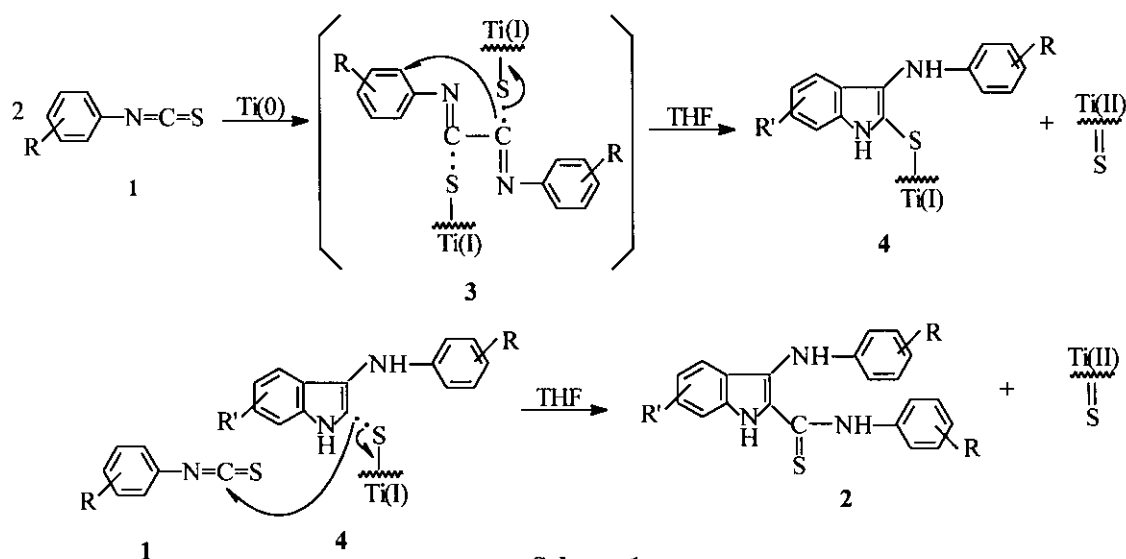
**Table 1.** Preparation of **2**

| 1  | R (1)               | 2   | R (2)               | R' (2)              | Yield(%) |
|----|---------------------|-----|---------------------|---------------------|----------|
| 1a | H                   | 2a  | H                   | H                   | 44       |
| 1b | 2-CH <sub>3</sub>   | 2b  | 2-CH <sub>3</sub>   | 7-CH <sub>3</sub>   | 11       |
| 1c | 4-CH <sub>3</sub>   | 2c  | 4-CH <sub>3</sub>   | 5-CH <sub>3</sub>   | 32       |
| 1d | 4-Cl                | 2d  | 4-Cl                | 5-Cl                | 23       |
| 1e | 3-CH <sub>3</sub> O | 2e  | 3-CH <sub>3</sub> O | 6-CH <sub>3</sub> O | 19       |
|    |                     | 2e' | 3-CH <sub>3</sub> O | 4-CH <sub>3</sub> O | 7        |

Isothiocyanates (**1a-e**) were easily prepared from the corresponding amines following a known procedure.<sup>4</sup> As shown above, reductive cyclizations of isothiocyanates (**1a-e**) with  $\text{TiCl}_4\text{-Zn}$  in the presence of THF afforded 3-arylamino-1*H*-indole-2-(*N*-aryl)carbothioamides (**2a-f**).

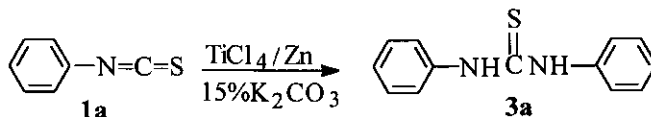
Figure 1. X-Ray crystal structure of **2a**

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



Isothiocyanates (**1**) are reductively dimerized with an initial formation of vicinal dithiomidate 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%).



The formation of the indoles was confirmed unambiguously by a singlecrystal X-Ray analysis of **2a**, and the result of X-Ray crystallographic analysis is depicted in Figure 1.<sup>5</sup>

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.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -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  $\text{TiCl}_4$  (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%  $\text{K}_2\text{CO}_3$  solution and extracted with  $\text{CHCl}_3$ . The combined organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$  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-phenyl)carbothioamides (2a):** mp 190-192°C; IR (KBr) $\text{cm}^{-1}$ : 3300, 3250-3150, 1590, 1560, 1520, 1490;  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =5.40(s, 1H, NH), 6.74-7.73(m, 14H, ArH), 9.50(s, 1H, NH), 12.04(s, 1H, NHCS).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$ =112.3, 115.7, 120.2, 120.9, 121.3, 122.7, 122.8, 125.6, 126.2, 128.3, 128.8, 129.7, 130.3, 135.1, 138.9, 145.6, 183.8. MS(EI): 343( $\text{M}^+$ ), 310, 250, 218, 135. Anal. Calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_3\text{S}$ : C 73.44, H 4.99, N 12.23, S 9.33. Found: C 73.94, H 5.09, N 12.41, S 9.42.

**3-(2-Methylphenylamino)-7-methyl-1H-indole-2-(N-2-methylphenyl)carbothioamides (2b):** mp 160-162°C; IR (KBr) $\text{cm}^{-1}$ : 3350, 3250-3150, 1600, 1580, 1545, 1495;  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =2.09(s, 3H,  $\text{CH}_3$ ), 2.43(s, 3H,  $\text{CH}_3$ ), 2.55(s, 3H,  $\text{CH}_3$ ), 6.57-7.44(m, 11H, ArH), 7.77(s, 1H, NH), 9.52(s, 1H, NH), 11.49(s, 1H, NHCS).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$ =11.7, 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( $\text{M}^+$ ), 352, 278, 149. Anal. Calcd for  $\text{C}_{24}\text{H}_{23}\text{N}_3\text{S}$ : C 74.77, H 6.01, N 10.90. Found: C 75.05, H 6.16, N 10.73.

**3-(4-Methylphenylamino)-5-methyl-1H-indole-2-(N-4-methylphenyl)carbothioamides (2c):** mp 208-209°C; IR (KBr) $\text{cm}^{-1}$ : 3350, 3150-3100, 1610, 1595, 1545, 1525, 1500;  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =2.25(s, 3H,  $\text{CH}_3$ ), 2.30(s, 3H,  $\text{CH}_3$ ), 3.32(s, 3H,  $\text{CH}_3$ ), 5.27(s, 1H, NH), 6.65-7.62(m, 11H, ArH), 9.44(s, 1H, NH), 12.08(s, 1H, NHCS).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$ =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( $\text{M}^+$ ), 352, 278, 245, 149. Anal. Calcd for  $\text{C}_{24}\text{H}_{23}\text{N}_3\text{S}$ : C 74.77, H 6.01, N 10.90. Found: C 75.23, H 6.01, N 10.99.

**3-(4-Chlorophenylamino)-5-chloro-1H-indole-2-(N-4-chlorophenyl)carbothioamides (2d):** mp 231-233°C; IR (KBr) $\text{cm}^{-1}$ : 3300, 3250-3150, 1610, 1600, 1550, 1495;  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =6.84-7.85(m, 11H, ArH),  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$ =115.3, 117.7, 119.9, 124.8, 125.7, 126.4, 126.6, 129.3, 130.0, 145.9. MS(EI): 445( $\text{M}^+$ ), 412, 378, 318, 276, 241, 206, 169, 111. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{N}_3\text{Cl}_2\text{S}$ : C 56.46, H 3.16, N 9.41. Found: C 56.72, H 3.09, N 9.18.

**3-(3-Methoxyphenylamino)-6-methoxy-1H-indole-2-(N-3-methoxyphenyl)carbothioamides (2e):** mp 177-179°C; IR (KBr) $\text{cm}^{-1}$ : 3300, 3150, 1620, 1600, 1560, 1520, 1490;  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =3.68(s, 3H,  $\text{OCH}_3$ ), 3.73(s, 3H,  $\text{OCH}_3$ ), 3.80(s, 3H,  $\text{OCH}_3$ ), 5.49(s, 1H, NH), 6.36-7.57(m, 11H, ArH), 9.34(s, 1H, NH), 11.79(s, 1H, NHCS).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$ =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,

159.3, 159.9, 161.1, 183.0. MS(EI): 433(M<sup>+</sup>), 400, 310, 268, 165, 122. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>S: C 66.49, H 5.35, N 9.69. Found: C 66.55, H 5.35, N 9.70.

3-(3-Methoxyphenylamino)-4-methoxy-1*H*-indole-2-(*N*-3-methoxyphenyl)carbothioamides (**2e'**): mp 167-168°C; IR(KBr)cm<sup>-1</sup>: 3330, 3150, 1600, 1550, 1520, 1480; <sup>1</sup>H-NMR(90 MHz, CDCl<sub>3</sub>): δ=3.68(s, 3H, OCH<sub>3</sub>), 3.71(s, 3H, OCH<sub>3</sub>), 3.74(s, 3H, OCH<sub>3</sub>), 5.97(s, 1H, NH), 6.34-7.44(m, 11H, ArH), 9.46(s, 1H, NH), 11.64(s, 1H, NHCS). <sup>13</sup>C-NMR(CDCl<sub>3</sub>): 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<sup>+</sup>), 400, 310, 268, 165, 122. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>S: C 66.49, H 5.35, N 9.69. Found: C 66.72, H 5.32, N 9.30.

**General Procedure for Compound (3a).**- To a dry 100mL flask charged with **1** (15 mmol) and zinc dust (2.60 g, 40 mmol), was added 2.2 mL (20 mmol) TiCl<sub>4</sub> 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 CHCl<sub>3</sub> (50 mL×3). The combined CHCl<sub>3</sub> extract was washed with water (30 mL×3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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.,<sup>8</sup> 154 °C).

## ACKNOWLEDGMENT

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5. Yellow plate single crystals suitable for X-Ray diffraction analysis were obtained from ethyl acetate-petroleum ether(60-90°C): Space group P2<sub>1</sub>/c, a=13.991(1), b=5.748(1), c=21.569Å; β=90.619(8)°, Z=4.1619 reflection obtained, R=0.034, R<sub>w</sub>=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: CF1106.
6. All the peaks of the labile protons disappeared after the addition of the D<sub>2</sub>O.
7. As there was a little of H<sub>2</sub>O in the system, the peaks of the labile protons did not appear.
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