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

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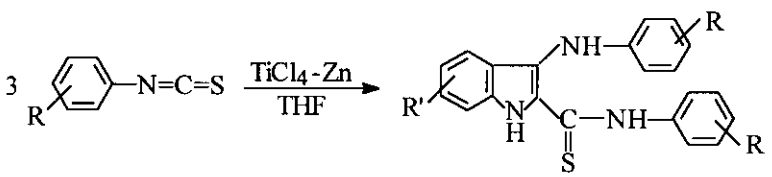
Abstract - Reductive cyclization of aryl isothiocyanates (**1**) induced by titanium tetrachloride - zinc provides a synthesis of substituted indol-2-carbothioamides(**2**).

The reductive coupling of carbonyl compounds with low-valent titanium reagents constitutes an attractive route to alkenes, which has found considerable application in synthesis. [1] 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[2] and the reductive coupling of phenyl isocyanate to afford substituted urea and biurea. [3] Herein, we present our preliminary results on the synthesis of substituted indole-2-carbothioamides (**2**) using a reductive cyclization of isothiocyanates by $TiCl_4$-Zn.



1 **2**

Table 1. Preparation of **2**

1	R (1)	2	R (2)	R' (2)	Yield(%)
1a	H	2a	H	H	44
1b	2-CH_3	2b	2-CH_3	7-CH_3	11
1c	4-CH_3	2c	4-CH_3	5-CH_3	32
1d	4-Cl	2d	4-Cl	5-Cl	23
1e	3-CH_3O	2e	3-CH_3O	6-CH_3O	19
		2e'	3-CH_3O	4-CH_3O	7

Isothiocyanates (**1a-e**) were easily prepared from the corresponding amines following a known procedure.[4] As shown above, reductive cyclizations of isothiocyanates (**1a-e**) with $TiCl_4$-Zn in the presence of THF afforded 3-arylamino-1*H*-indole-2-(*N*-aryl)carbothioamides (**2a-f**).

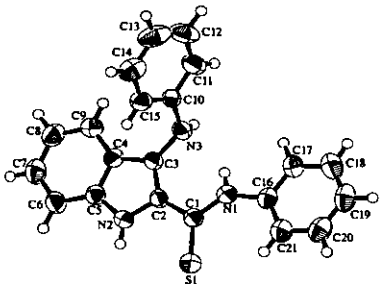
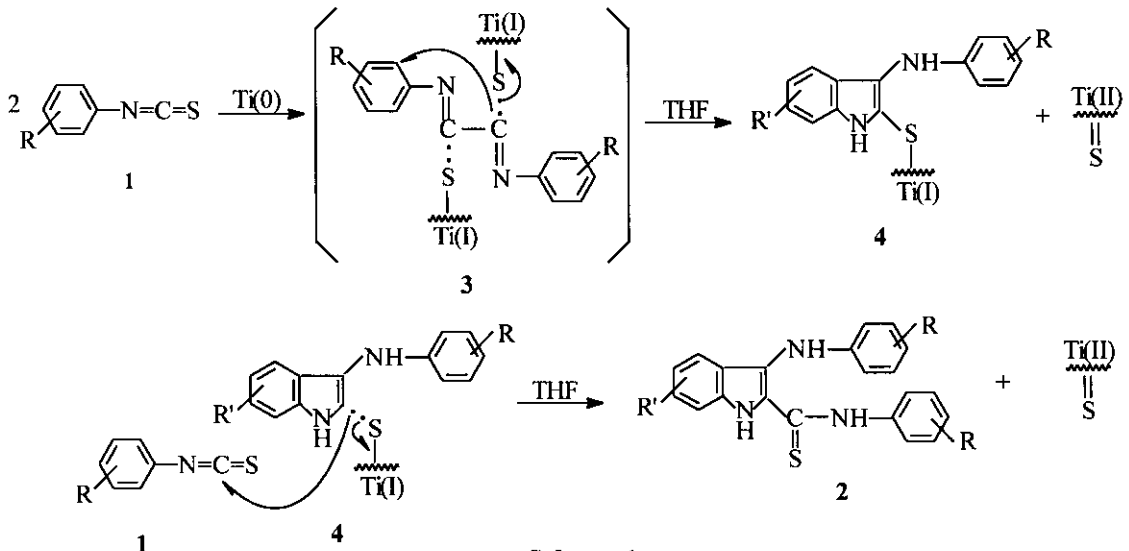


Figure 1. X-Ray crystal structure of **2a**

The 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.[5]

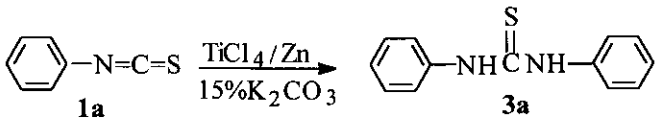
The mechanism of the reaction may be postulated as Scheme 1.



Scheme 1

Isothiocyanates (**1**) are reductivity 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%).



1a **3a**

In conclusion, our work extented 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 stardard. 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_2CO_3 solution and extracted with $CHCl_3$. The combined organic layer was washed with water, dried over Na_2SO_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 recrystalled from benzene, yellow needles crystal was obtained (1.51 g, 44%). The procedures of other derivatives are similar to above.

3-Phenylamino-1*H*-indole-2-(*N*-phenyl)carbothioamides (**2a**): mp 190-192°C; IR (KBr)cm^{-1}: 3300, 3250-3150, 1590, 1560, 1520, 1490; ^{1}H-NMR(90 MHz, $CDCl_3$): δ=5.40(s, 1H, NH),[6] 6.74-7.73(m, 14H, ArH), 9.50(s, 1H, NH), 12.04(s, 1H, NHCS). ^{13}C-NMR($CDCl_3$): δ=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(M$^+$), 310, 250, 218, 135. Anal. Calcd for $C_{21}H_{17}N_3S$: 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-1*H*-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, $CDCl_3$): δ=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($CDCl_3$): δ=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(M$^+$), 352, 278, 149. Anal. Calcd for $C_{24}H_{23}N_3S$: C 74.77, H 6.01, N 10.90. Found: C 75.05, H 6.16, N 10.73.

3-(4-Methylphenylamino)-5-methyl-1*H*-indole-2-(*N*-4-methylphenyl)carbothioamides (**2c**): mp 208- 209 °C; IR (KBr)cm^{-1}: 3350, 3150-3100, 1610, 1595, 1545, 1525, 1500; ^{1}H-NMR(90 MHz, $CDCl_3$): δ=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($CDCl_3$): δ=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. Calcd for $C_{24}H_{23}N_3S$: C 74.77, H 6.01, N 10.90. Found: C 75.23, H 6.01, N 10.99.

3-(4-Chlorophenylamino)-5-chloro-1*H*-indole-2-(*N*-4-chlorophenyl)carbothioamides (**2d**): mp 231- 233 °C; IR(KBr)cm^{-1}: 3300, 3250-3150, 1610, 1600, 1550, 1495; ^{1}H-NMR(90 MHz, $CDCl_3$)[7]: δ=6.84-7.85(m, 11H, ArH), ^{13}C-NMR($CDCl_3$): δ=115.3, 117.7, 119.9, 124.8, 125.7, 126.4, 126.6, 129.3, 130.0, 145.9. MS(EI): 445(M$^+$), 412, 378, 318, 276, 241, 206, 169, 111. Anal. Calcd for $C_{21}H_{14}N_3Cl_3S$: C 56.46, H 3.16, N 9.41. Found: C 56.72, H 3.09, N 9.18.

3-(3-Methoxyphenylamino)-6-methoxy-1*H*-indole-2-(*N*-3-methoxyphenyl)carbothioamides (**2e**): mp 177-179 °C; IR (KBr) cm^{-1}: 3300, 3150, 1620, 1600, 1560, 1520, 1490; ^{1}H-NMR(90 MHz, $CDCl_3$): δ=3.68(s, 3H, OCH_3), 3.73(s, 3H, OCH_3), 3.80(s, 3H, 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}C-NMR($CDCl_3$): δ=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^+), 400, 310, 268, 165, 122. Anal. Calcd for $C_{24}H_{23}N_3O_3S$: 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^{-1}: 3330, 3150, 1600, 1550, 1520, 1480; ^{1}H-NMR(90 MHz, $CDCl_3$): δ=3.68(s, 3H, OCH_3), 3.71(s, 3H, OCH_3), 3.74(s, 3H, OCH_3), 5.97(s, 1H, NH), 6.34-7.44(m, 11H, ArH), 9.46(s, 1H, NH), 11.64(s, 1H, NHCS). ^{13}C-NMR($CDCl_3$): 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 $C_{24}H_{23}N_3O_3S$: 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) $TiCl_4$ 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 $CHCl_3$ (50 mL×3). The combined $CHCl_3$ extract was washed with water (30 mL×3), dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The crude product was recrystalled with ethanol and yellow plate crystal was obtained (3.10 g, 91%, mp 154-156 °C lit.,[8] 154 °C).

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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 $P2_1/c$, 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: CF1106.
6. All the peaks of the labile protons disappeared after the addition of the D_2O.
7. As there was a little of H_2O in the system, the peaks of the labile protons did not appear.
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