SYNTHESIS AND CHARACTERISATION OF NOVEL CHIRAL THIOUREA DERIVATIVES AS POTENTIAL BIOLOGICAL ACTIVE AGENTS

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Abstract

N-Boc-Chiral amide derivatives (2a-b) were prepared from amino acids (L-Iso-Leucine and L-Valine) and 2-Aminophenol. After deprotection of these compounds with phosphoric acid (H_3PO_4-85%), deprotected amides (3a-b) were obtained and reacted with benzoyl isothiocyanide to give potentially biological active thiourea derivatives (4a-b). The structures of the compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR.

Keywords: Chiral thiourea, biological activity, asymmetric synthesis.

Introduction

Acyl substituted thiourea derivatives are important intermediates in organic synthesis and possess various biological activities[1].

The development of new antimicrobial and anti cancer therapeutic agents is one of the fundamental goals in medicinal chemistry. Chiral thioureas and their derivatives display a wide range of biological activities such as antibacterial, antiviral and antifungal[2].

In addition, some of these compounds could be used as catalysts in asymmetric reactions such as the Michael addition to nitroalkenes and the Biginelli reaction. The Michael addition to electron deficient nitroolefins is one of the important reactions in organic synthesis that provides access to synthetically useful nitroalkanes. The Biginelli reaction, which is a three-component reaction of an aromatic aldehyde, urea and acetoacetate, is one of the most efficient methods for the assembly of heterocyclic compounds[3]. Therefore, recent efforts have been devoted to the synthesis of these compounds [4-5]. In the light of this information, novel chiral thioureas bearing amino acids and 2-aminophenol moieties were synthesized in good yields and the structures of the compounds were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR.

Experimental

All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. IR spectra were recorded on a Perkin Elmer 100 FTIR spectrometer. Solvents were used as received from commercial sources.

Preparation of N-Boc-Amide Derivatives (2a-b)

To a solution of N-Boc-amino acid (**1a-b**) (1 mmol) in 15 ml THF were added 2-aminophenol (1 mmol) and a slight excess of DCC (N,N'-Dicyclohexylcarbodiimide) (1.2 mmol). The mixture was stirred under inert atmosphere at room temperature overnight. The insoluble dicyclohexylurea was removed by filtration and the solvent was evaporated. Evaporation of the solvent was provided a residue which was purified by column chromatography using DCM (Dichloromethane) and Methanol (25:1).

(2a): Yellow oily product, 73% yield, IR (KBr): 3291.1, 3070.7, 2970.5, 2934.3, 2875.3, 1689.1, 1680.3, 1612.9, 1600.5, 1532.1, 1505.8, 1499.1, 1367.8, 1286.4, 1245.8, 1169.6, 1043.1, 1018.8 and 749.9. ^{1}H NMR ($CDCl_3$, δ ppm) 8.67 (s, 1H), 8.59 (bs, 1H), 7.08 (d, *J*= 8 Hz, 2H), 6.98 (dd, *J*= 8.4 Hz and 1.2 Hz, 1H), 6.82 (td, *J*= 8 Hz and 1.2 Hz, 1H), 5.19 (d, *J*= 8 Hz, 1H), 4.42 (t, *J*= 7.2 Hz, 1H), 2.24 (m, 1H), 1.46 (s, 9H), 1.05 (d, *J*= 6.4 Hz, 3H) and 1.01 (d, *J*= 6.8 Hz).^{13}C NMR ($CDCl_3$, δ ppm) 172.1, 156.7, 153.8, 148.8, 127.2, 125.5, 122.7, 120.6, 60.9, 31.1, 28.5, 28.5, 19.5 and 18.4.

(2b): Yellow oily product, 53% yield, IR (KBr): 3291.9, 3049.5, 2965.2, 2933.3, 2857.4, 1694.4, 1660.5, 1524.3, 145.9, 1392.5, 1349.1, 1340.5, 1256.9, 1168.0, 1019.3, 893.9 and 738.2. ^{1}H NMR ($CDCl_3$, δ ppm) 8.74 (bs, 1H), 7.08 (m, 2H), 6.98 (d, *J*= 7.6 Hz, 1H), 6.79 (t, *J*= 7.2 Hz, 1H), 5.73 (d, *J*= 8 Hz, 1H), 4.18 (m, 1H), 1.96 (m, 1H), 1.6 (m, 1H), 1.44 (s, 9H), 1.01 (d, *J*= 6.8 Hz, 3H), 0.93 (d, *J*= 7.6 Hz, 3H).

Deprotection of Protected Amides (3a-b)

1 mmol N-Boc-amide (**2a-b**) was dissolved in 2 ml THF and 2 ml 85% H_3PO_4 was added dropwise to the solution. The reaction mixture was stirred overnight at room temperature. To terminate the reaction, 5 ml distilled water was added and the reaction mixture was neutralized with saturated NaOH. The solution was extracted with Ethyl acetate. The organic phase was dried using Na_2SO_4 and evaporated under vacuum and yellow solid and oily products were obtained.

3a): Yellow solid, 77% yield, mp = 140-142ºC, IR (KBr): 3411.9, 3329.2, 2966.4, 2918.8, 2707.5, 1676.4, 1596.7, 1525.7, 1456.0, 1396.5, 1284.9, 1259.6, 1004.3, 751.3 and 562.3. ^{1}H NMR ($CDCl_3$, δ ppm) 9.81 (s, 1H), 7.11 (td, *J*= 8.4 Hz and 1.2 Hz, 1H), 7.02 (dd, *J*= 8 Hz and 1.2 Hz, 1H) 6.95 (dd, *J*= 8 Hz and 1.6 Hz, 1H), 6.84 (td, *J*= 8.8 Hz and 1.6 Hz, 1H), 3.47 (d, *J*= 3.6 Hz, 1H), 2.46 (m, 1H), 1.07 (d, *J*= 7.2 Hz, 3H) and 0.9 (d, *J*= 6.8 Hz, 3H), ^{13}C NMR ($CDCl_3$, δ ppm) 151.3, 148.9, 127.3, 125.5, 122.3, 120.55, 59.9, 30.9, 28.5, 24.8 and 19.5.

(3b): Yellow oily product, 85% yield, IR (KBr): 3287.0, 2963.9, 2876.2, 2733.7, 1695.6, 1596.5, 1499.3, 1428.9, 1282.9, 1105.5, 750.9 and 651.4. ^{1}H NMR ($CDCl_3$, δ ppm), 9.81 (bs, 1H), 7.12 (td, *J*= 8 Hz and 1.6 Hz, 1H), 7.02 (d, *J*= 8 Hz, 1H), 6.95 (d, *J*= 6.8 Hz, 1H), 6.84 (td, *J*= 7.2 Hz and 0.8 Hz,1H), 3.52 (d, *J*= 3.6 Hz, 1H), 2.16 (m, 2H), 2.09 (s, 1H), 1.37 (m, 1H), 1.15 (m, 1H), 1.05 (d, *J*= 6.8 Hz, 3H) and 0.93 (t, 7.6 Hz, 3H).^{13}C NMR ($CDCl_3$, δ ppm) 174.8, 173.7, 149.4, 127.3, 125.4, 122.3, 120.2, 59.7, 38.2, 23.9, 15.3 and 12.2.

Thiourea Reaction of Deprotected Amide (4a-b)

0.25 mmol potassium thiocyanide (KSCN) was stirred in 10 ml dried acetone and benzoyl chloride was added dropwise under an argon atmosphere. Precipitation was observed immediately. The reaction mixture was refluxed until the color of the solution turned yellow (approximately 2h). Then the reaction mixture was cooled to room temperature and an amide (**3a-b**) solution in 5 ml dried acetone was added dropwise to the reaction flask which was then refluxed for 2h. Reaction was monitored by TLC. The solution was filtered and evaporation of the solvent from the filtrate provided a residue which was crystallized from DCM: hexane to give bright yellow crystals.

(4a): Bright yellow crystal, 79% yield, mp = 164.5-165.8ºC, IR (KBr): 3308.1, 3248.7, 2968.9, 2981.5, 2892.1, 1670.2, 1645.9, 1531.6, 1453.0, 1392.5, 1371.8, 1306.0, 1263.6, 1162.3, 1093.0, 748.4, 714.1 and 612.0. ^{1}H NMR ($CDCl_3$, δ ppm) 11.23 (d, *J*= 7.2 Hz, 1H), 9.11 (s, 1H), 8.44 (s, 1H), 7.84 (d, *J*= 7.6 Hz, 2H), 7.64 (t, *J*= 1.2 Hz, 1H), 7.52 (t, *J*= 8 Hz, 2H), 7.17 (d, *J*= 1.6 Hz,1H), 7.14 (t, *J*= 6.8 Hz, 1H), 7.09 (d, *J*= 1.6 Hz, 1H), 6.87 (t, *J*= 6.8 Hz, 1H), 4.93 (t, *J*= 7.2 Hz, 1H), 2.52 (m, 1H) and 1.15 (d, *J*= 6.8 Hz, 6H).^{13}C NMR ($CDCl_3$, δ ppm) 169.7, 167.3, 148.7, 134.1, 131.6, 129.4, 127.8, 127.4, 125.4, 122.9, 120.8, 119.4, 65.7, 30.6, 19.6 and 18.6.

(4b): Yellow solid, 79% yield, mp = 161-163 ºC, IR (KBr): 3269.1, 3148.2, 3063.7, 2961.1, 2927.2, 2877.1, 1666.8, 1599.3, 1580.3, 1498.1, 1458.2, 1351.3, 1302.8, 11.3¸1157.5, 1084.1, 745.5, 723.4 and 602.8. ^{1}H NMR ($CDCl_3$,δ ppm) 11.22 (d, *J*= 7.6 Hz, 1H), 9.09 (s, 1H), 8.4 (s, 1H), 8.29 (bs, 1H), 7.86 (d, *J*= 8 Hz, 2H), 7.64 (t, *J*= 7.2 Hz, 1H), 7.53 (t, *J*= 8 Hz, 2H), 7.12 (t, *J*= 7.6 Hz, 2H), 7.08 (d, *J*= 7.2 Hz,1H), 6.86 (t, *J*= 7.6 Hz, 1H), 4.99 (t, *J*= 7.6 Hz, 1H), 2.32 (m, 1H), 1.72 (m, 1H), 1.67 (s, 1H), 1.40 (m, 1H), 1.11 (d, *J*= 6.8 Hz, 3H) and 1.01 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, δ ppm), 181.3, 169.7, 167.3, 148.8, 134.1, 131.6, 129.4, 127.8, 127.5, 125.4, 122.9, 120.8, 119.6, 64.7, 36.5, 25.4, 15.9 and 11.4.

Result and Discussion

In this work N-Boc-amino acids were reacted with 2-Aminophenol to obtain N-Boc-chiral amide derivatives (**2a-b**) in the presence of DCC (N,N'-Dicyclohexylcarbodiimide). These reactions were carried out at room temperature and the products were obtained in good yield.

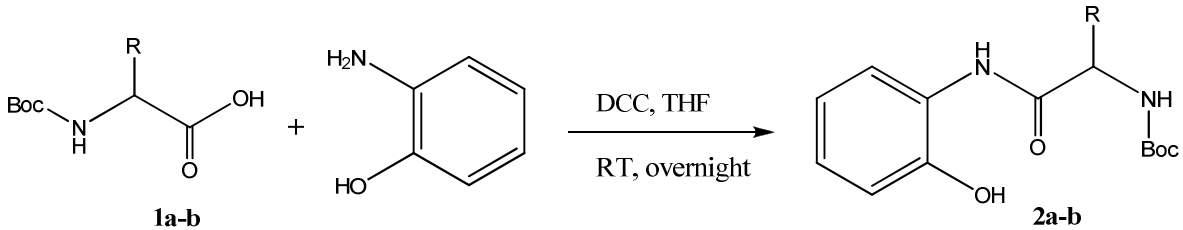

Figure 1. Synthesis of N-Boc-Amide Derivatives

After this reaction, deprotection occurred with H_3PO_4 (85%) and deprotected amides (**3a-b**) were obtained in excellent yield.

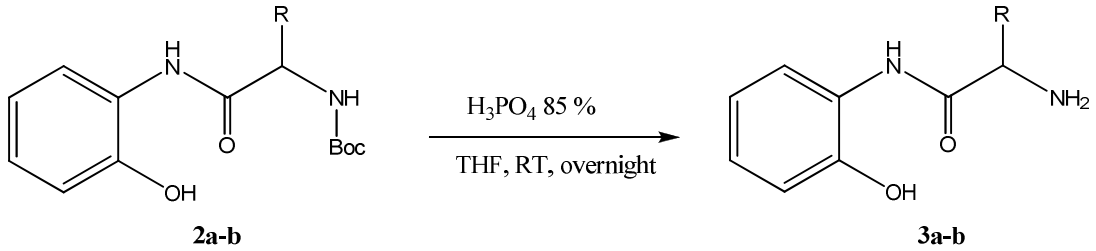

Figure 2. Deprotection of N-Boc-Amide Derivatives

The deprotected amides were reacted with benzoyl isothiocyanide which was freshly prepared from benzoyl chloride and potassium thiocyanide. In this reaction, amine groups act as nucleophiles and attack the thiocarbonyl side of the benzoyl isothiocyanide. Subsequent rearrangement leads to the

desired thiourea derivatives (**4a-b**) which were obtained in good yields.

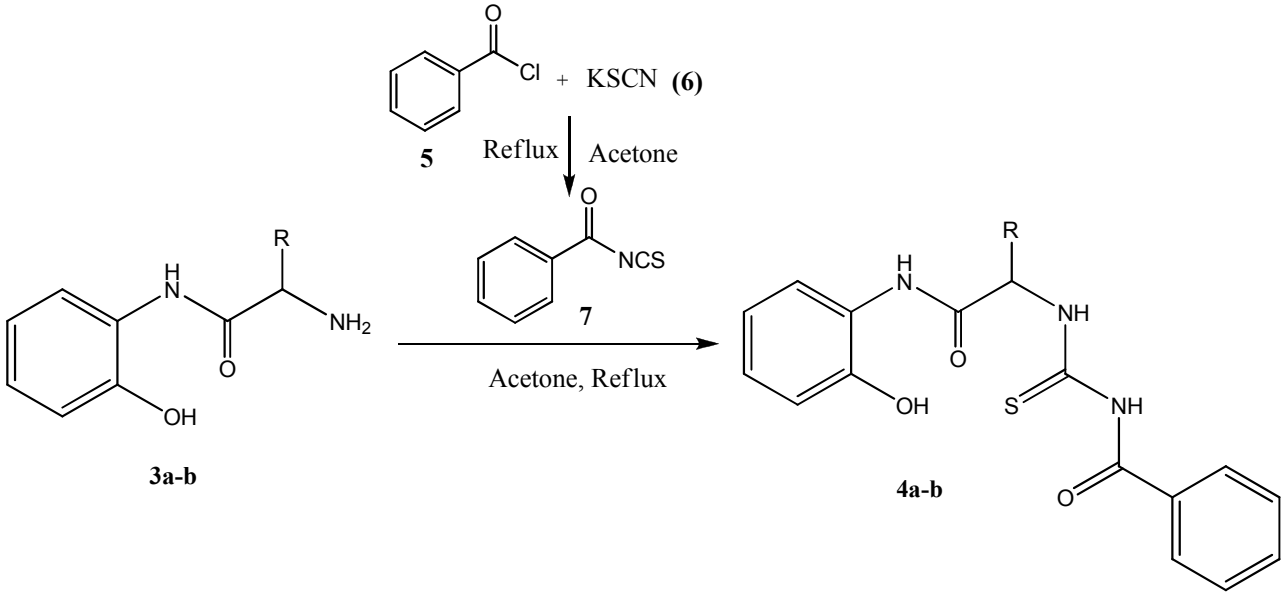

Figure 3. Synthesis of Chiral Thiourea Derivative

This work still continues and different thiourea derivatives are going to be synthesised and their biological and catalytic activities are going to be analysed.

Conclusion: Potentially biological and catalytically active 2 novel chiral thiourea derivatives were synthesised in very good yields. All compounds were characterized by spectroscopic methods.

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