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Synthesis of 2,2-Dithiobisbenzamides Derivatives

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2,2-Dithiosalicylic acid was converted into its pseudo amino acid *via* the formation of the anhydride followed by a Curtius rearrangement. An amino acid derived dithiolactam was also synthesized by coupling the corresponding bis-acid chloride with ethyl glycinate and subsequent Curtius rearrangement. A carboxy-protected pseudo amino acid was also prepared.

Key Words: Synthesis, Characterization, 2,2-Dithiobisbenzamides derivatives.

INTRODUCTION

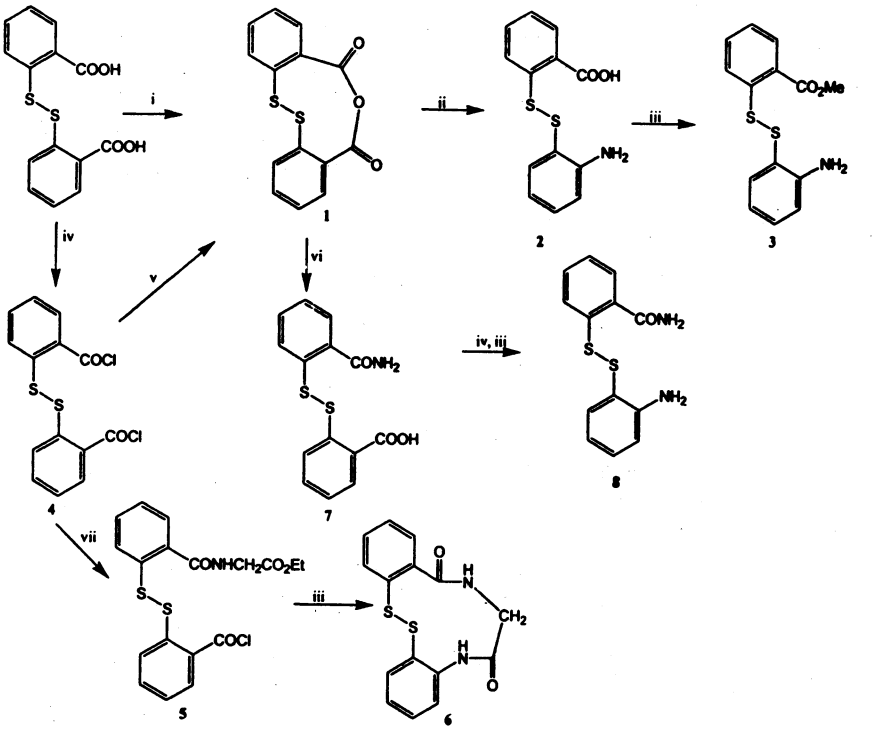
2,2-Dithiobisbenzamide derivatives have been reported to possess important biological properties[1-5]such as antibacterial, antifungal activities and inhibition of blood platelet aggregation. Recently, 2,2-dithiobisbenzamides[6-10] have been classified as a new class of anti-HIV agents which was found to possess anti-HIV activity at low micromolar to submicromolar concentrations. These compounds were found to inhibit both laboratory strains and clinical isolates of HIV-1, including strains resistant to the nucleoside inhibitor 3-azido-3′-deoxythymidine (AZT) or to neviparine. Herein, the synthesis of some derivatives of 2,2-dithiobisbenzamides have been reported..

EXPERIMENTAL

Infrared spectra (IR) were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer in the range of 4000–400 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Spectrospin at 250 MHz with TMS as internal standard in DMSO-d_6 as solvent. Elemental analyses were performed on a LECO CHNS-932 analyzer. Melting points were determined on an electrothermal digital melting point apparatus. The chemicals used were of analytical grade.

2,2′-Dithiosalicylic anhydride (1)

2,2′-Dithiosalicylic acid (0.753 g, 2.46 mmol) was refluxed for 1 h with excess acetic anhydride (10 mL). The reaction was monitored by TLC (EtOAc). A clear reddish brown solution was obtained. The excess of acetic anhydride was



Scheme-1

Conditions: (i) Ac_2O, (ii) heat: NaN_3; (iii) Conc. H_2SO_4, MeOH; (iv) $SOCl_2$; (v) K_2CO_3; (vi) conc. NH_3; (vii) glycine ester.

evaporated and trace of acetic anhydride was removed azeotropically with toluene. A brown mass was obtained. Petroleum ether was added to the brown mass and the brown solid was filtered. The crude product was recrystallized from toluene to yield the anhydride as a pale brown powder in 90% (1.560 g) yield, m.p. 234°C; IR (nujol, cm^{-1}): 1797 ν(C=O), 1716 ν(C=O), ^1H NMR δ 8.0 (d, J = 7.5 Hz, 2H), 7.6 (d, J = 8 Hz, 2H), 7.5 (t, J = 7.5 Hz, 2H), 7.3 ppm (t, J = 7 Hz, 2H); ^{13}C NMR δ 172.5, 168.1, 139.5, 133.8, 132.1, 128.6, 126.5, 125.5 ppm.

Amino-diphenyldisulphide carboxylic acid (2)

Sodium azide was added to a suspended solution of the anhydride **1** (0.615 g, 2.08 mmol) in chlorofonn (20 mL) and the mixture was refluxed for 4 h. The brown precipitate was filtered and washed with water to yield the pure product in 54% yield (0.330 g), m.p. 284°C; IR (nujol, cm^{-1}): 3386 (broad band, ν(OH) and ν(NH), 1662 ν(C=O); ^1H NMR δ 8.3 (2H), 7.9 (d, J = 7 Hz, 2H), 7.4 (d, J = 8 Hz), 7.2 (t, J = 7 Hz, 2H), 7.1 ppm (t, J = 7 Hz, 2H). Positive Lassaigne test for nitrogen was observed.

Amino-diphenyldisulphide methylester (3)

Concentrated sulphuric acid (5 mL) was added to a suspension of **2** (0.198 g, 0.684 mmol) in methanol (20 mL) and the reaction mixture was refluxed for 2 h. The mixture was then neutralized with concentrated ammonia and the precipitate formed was filtered and dried. A pale brown solid (0.137 g, 66%), was obtained, m.p. 180°C (with decomposition); IR (nujol, cm^{-1}): 1705 ν(C=O); ^1H NMR δ 8.0 (d, J = 7 Hz), 7.6 (m, 4H), 7.4 (m, 2H), 3.9 (s, 3H); ^{13}C-NMR δ 166.6, 139.4, 139.1, 134.2, 133.8, 132.1, 131.9, 128.6, 127.5, 126.8, 127.5, 126.8, 126.6, 126.5, 125.4, 53.1 ppm. Positive Lassaigne test for nitrogen was observed.

Ethyl glycinate

To a solution of L-glycine (2.534 g, 0.034 mol) in absolute ethanol (25 mL), concentrated sulphuric acid (3 mL) was added. The reaction mixture was refluxed for 2 h. The reaction mixture was neutralized with concentrated ammonia and the white precipitate formed was filtered and washed with aqueous ethanol. The product was obtained as a white solid (1.883 g, 54%), m.p. 180-183°C; IR (nujol, cm^{-1}): 1666 ν(C=O); ^1H NMR δ 4.1 (q, J = 7 Hz, 2H), 3.6 (s, 2H), 1.2 ppm (t, J = 7 Hz, 3H).

1,1′-Diphenyldisulphidethylglycinatemethanoyl chloride (5)

To a solution of bis-acid chloride **4** (1.00 g, 2.91 mmol) in THF (20 mL) ethyl glycinate (0.30 g, 2.91 mmol) and triethylamine (0.5 mL) were added. The reaction mixture was refluxed for 1 h; IR (neat, cm^{-1}): 1766 ν(C=O); 1720 ν(C=O); 1674 ν(C=O).

4,6,7-Trihydro-[c,i]-dibenzo[1,2,5,8]-dithiadiazadecine-5,8-dione (6)

To the reaction mixture containing **5** in chloroform (30 mL) sodium azide (0.38 g, 5.82 mmol) was added and the reaction mixture was refluxed for 2 h. The reaction was monitored by TLC (EtOAc). The reaction mixture was filtered and washed with water. The residue was then washed with hot methanol, followed by dilute hydrochloric acid, saturated sodium hydrogen carbonate solution and with water. The product was obtained as a pale brown solid (0.540 g, 64%), m.p. 190°C; IR (nujol, cm^{-1}): 1679 ν(C=O), 1709 ν(C=O), ^1H NMR δ 8.1 (d, N—H, 2H), 8.0 (d, J = 7.5 Hz, 2H), 7.6 (m, 4H), 7.3 (t, J = 7 Hz, 2H), 3.9 (s, 2H); ^{13}C-NMR δ 168.2, 168.1, 139.4, 133.8, 132.1, 128.6, 126.6, 126.5, 125.5, 80.0 ppm. Positive Lassaigne test for nitrogen was observed.

1,1′-Carboxyl-diphenyldisulphideamide (7)

The anhydride **2** (0.942 g, 3.27 mmol) was dissolved in concentrated ammonia (40 mL) and the reaction mixture was refluxed for 2 h. The reaction was monitored by TLC (EtOAc). When the reaction mixture was neutralized with dilute hydrochloric acid, a pale brown precipitate was formed which was filtered and recrystallized from aqueous ethanol. The product was obtained as a pale brown powder (0.743 g, 75%), m.p. 245–247°C; IR (nujol, cm^{-1}): 3400 ν(NH) and ν(OH), 1682 ν(C=O), 1643 ν(C=O), ^1H NMR δ 8.1 (COOH), 8.0 (d, J = 7 Hz, NH_2), 7.7–7.3 ppm (m, 8H).

1,1-Amino-diphenyldisulphideamide (8)

To a solution of **7** (0.214 g, 0.7 mmol) in THF (15 mL) thionyl chloride (0.1 mL) was added and the reaction mixture was refluxed for 1 h. IR (neat, cm^{-1}): 1871 ν(C=O), 1678 ν(C=O). To this reaction sodium azide (0.092 g, 2 eq) was added without any purification. The reaction mixture was refluxed for 2 h and was monitored by TLC. On completion of the reaction, the precipitate was filtered and washed with water, followed by dilute hydrochloric acid and water. A pale brown solid (0.134 g, 69%) was obtained, m.p. 255–258°C; IR (nujol, cm^{-1}): 1678 ν(C=O), ^{1}H NMR δ 8.0 (d, $CONH_2$), 7.7–7.3 (m, 8H), 5.7 ppm (NH_2); ^{13}C-NMR δ 168.1, 139.4, 137.2, 133.8, 132.1, 128.6, 126.5, 125.5, 122.0 ppm.

RESULTS AND DISCUSSION

Dithiosalicylic acid was first converted into the corresponding anhydride **1** using acetic anhydride. The IR spectra of **1** showed 2 peaks at 1797 and 1716 cm^{-1} corresponding to the carbonyl stretching frequencies. The aromatic protons appeared at δ 7.4–8.0 ppm. The two carbonyl peaks in the ^{13}C NMR were at δ 172.5 and 168.1 ppm. The peaks at δ 139.5–125.5 ppm corresponded to the aromatic carbon atoms.

The anhydride was also synthesized by refluxing the bis-acid chloride with potassium carbonate in an aqueous medium.

The anhydride was opened up using sodium azide in chloroform. The NH_2 and OH peak of carboxylic merged and appeared as a broad peak at 3386 cm^{-1} in the IR spectrum of **2**. The peak at 1662 cm^{-1} corresponded to the carboxylate stretching frequency. The ^{1}H NMR spectrum of **2** showed peaks at δ 7.0–7.9 ppm corresponding to the aromatic protons and 8.3 ppm corresponding to the amine protons. Esterification of the amino acid **2** was performed in order to confirm the formation of compound **2**. The amino acid **2** was refluxed with methanol and concentrated sulphuric acid to yield the corresponding ester. The IR spectrum of ester **3** showed a peak at 1705 cm^{-1} relating to the ester stretching frequency. The ^{1}H–NMR spectrum showed aromatic protons at δ 7.4–8.1 ppm, the amino protons at δ 6.9 ppm and the methyl protons appeared as a singlet at δ 3.9 ppm. The ^{13}C NMR spectrum of **3** showed peaks at δ 166.6 ppm (C=O), 139.4–125.4 (12 aromatic carbons), 53 ppm (methyl carbon). The reaction of ethyl leucinate with **2** in the presence of DCC in DCM was unsuccessful, therefore an alternative strategy was employed.

2,2′-Dithiosalicylic acid was converted into the bis-acid chloride **4** using thionyl chloride. The bis-acid chloride was refluxed in THF with a mole equivalent of ethyl glycinate prepared by esterification of L-glycine to yield the dipeptide **5**. The IR spectrum of **5** showed peaks at 1766 cm^{-1} (C=O of acid), 1720 cm^{-1} (C=O of ester) and 1674 cm^{-1} (C=O of amide). Heating of the product in the presence of sodium azide gave the cyclized product **6**. The IR spectrum of compound **6** showed two carbonyl peaks at 1679 and 1709 cm^{-1} respectively. The ^{1}H NMR spectrum of **6** was consistent with the proposed structure and displayed peaks at δ 8.1 corresponding to N—H, at δ 7.3-8.0

corresponding to the aromatic protons and at δ 3.9 ppm corresponding to the methylene protons. No peaks were observed for the ethyl ester functionality, thus confirming that cyclization had occurred. The ^{13}C NMR spectrum was also consistent with the proposed structure with two carbonyl peaks at δ 168.1 and 168.2 ppm.

The anhydride **3** was dissolved in concentrated ammonia and the reaction mixture was refluxed for 2 h. On work-up **7** was obtained as a pale brown precipitate. The two carbonyl peaks appeared at 1682 cm^{-1} (carboxylic acid) and 1643 cm^{-1} (amide stretching frequency). The ^1H NMR spectrum of **7** showed peaks at δ 7.2–7.7 ppm (8 aromatic protons), at δ 7.9–8.0 ppm (doublet, NH_2), and at δ 8.1 ppm (carboxylic acid proton). Refluxing **7** with $SOCl_2$ followed sodium azide yielded compound **8**. The IR spectrum of the compound **8** formed showed a peak at 1678 cm^{-1}. The NH of the primary amide appeared at δ 8.0 whereas the amino peak appeared at δ 5.7 ppm. The ^{13}C NMR spectrum of **8** showed peaks at δ 168.1 ppm corresponding to the carbon atom of the amide group and at δ 122.0–139.4 ppm (12 aromatic carbon atoms). Thus, the data was consistent with the proposed structure for compound **8**.

This methodology can now be applied to introduce different amino groups in the diphenyldisulpide moiety.

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