SYNTHESIS OF NOVEL THIOSEMICARBAZIDE DERIVATIVES OF DISUBSTITUTED N-ARYLMALOEIMIDES.

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ABSTRACT

Herein we reported the synthesis of Thiosemicarbazide derivatives of disubstituted N-aryl maleimides. Maleimides are an important class of substrates for biological and chemical applications. The compound 1 were reacted with bromine in DMF to obtained the dibromosuccinimides 2 The compound 2 react with pyrrolidine, piperidine and morpholine as a base followed dehydrohalogenation to obtained monobromo compound; instead, complex mixtures of with unreacted dibromosccinimide 3a-c were obtained through common enaminone intermediate. Installation of an amino functionality at C-3 position in 3a-c should increase nucleophilicity at C-4 position. Thus Vilsmeier Haack formylation of 3a-c at 0-50°C afforded compound 4a-c with good yield. Thus condensation of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde 4 with thiosemicarbazide in ethanol in presence of acetic acid furnished orange colour solid 5 with good yield. All the synthesized compounds were characterized by spectral and analytical methods (IR, ¹H NMR, ¹³C NMR, Mass Spectroscopy and elemental analysis).

KEYWORDS: Malieimide, pyrrolidine, piperidine, morpholine and Thiosemicarbazon.
INTRODUCTION

Maleimide: Herein we reported the synthesis of Thiosemicarbazide derivatives of disubstituted N-arylmaleimides. Maleimide and its derivatives are synthesizes from maleic anhydride and amines followed by dehydration. Maleimides are an important class of substrates for biological and chemical applications. In biological applications they are used as chemical probes of protein structure, as immunoconjugates for cancer therapy, as solid supported enzymes for synthetic applications, as haptene for the production of antibodies or as new herbicides and pesticides. Cyclic imide shows potent analgesic action. Kalgutkar et al. have demonstrated that some N-substituted maleinimides inhibit the prostaglandin end peroxide synthase (PGHS). Frederic Zentz et al. reported the in vitro antibacterial and cytotoxic activities of 3-substituted succinimides. Maleimides shows a wide range of biological activities such as antibacterial and antifungal, antiprotozoal, antiangiogenic, analgesic, antistress agents, cytotoxic, DNA binding and apoptotic inducing activity. A biological property of these compounds includes angiogenesis inhibition, protein kinase inhibition, ant proliferative activity, and antimicrobial and antifungal properties.

Thiosemicarbazones are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones. Thiosemicarbazides is valuable building blocks for the synthesis of five-membered heterocycles. Thiosemicarbazones (hydrazine carbothioamides) are a family of compounds with beneficial biological activity. They are very good ligands, and it has been shown that their biological activity is related to their ability to coordinate to metal centers in enzymes. Thiosemicarbazones have received considerable attention because of their pharmacological activities. They have numerous biological activities, e.g., anticarcinogenic, antibacterial, anti-HIV, anticancer, fungicides, antiviral, antifungal, antitumor, etc. These compounds containing thione (C=S) and thiole (C-S) groups occupy an important position among organic reagents as potential donor ligands for transition metal ions. Thiosemicarbazones are potent intermediates for the synthesis of pharmaceutical and bioactive materials and thus, they are used extensively in the field of medicinal chemistry. Moreover, thiosemicarbazones have found their way into almost every branch of chemistry; commercially they are used as dyes, photographic films, plastic and in textile industry. These observations, increases our interest to synthesize new thiosemicarbazones due to their wide range of application in the field of organic and medicinal chemistry.
RESULTS AND DISCUSSION

Scheme-I

The compound 1 were reacted with bromine in DMF at 25-27 °C for 1-1.5 hrs. to obtained the dibromosuccinimides 2. The compound 2 react with pyrrolidine, piperidine and morpholine as a base followed dehydrohalogenation to obtained monobromo compound; instead, complex mixtures of with unreacted dibromosccinimide 3a-c were obtained through common enaminone intermediate. Installation of an amino functionality at C-3 position in 3a-c should increase nucleophilicity at C-4 position. 3a-c reacted with bromine in DMF at 0°C for 5 min. to give 4a-c. Vilsmeier Haack formylation of 3a-c at 0-5°C afforded compound 4a-c with good yield. (Scheme-1)

1H NMR Spectra of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde 4a.
$^{13}$C NMR Spectra of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde 4a.

**Scheme-II**

Thus condensation of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde 4 with thiosemicarbazide in ethanol in presence of acetic acid at 50°C furnished orange colour solid 5 with 88% yield. (Scheme-2). It was characterized by spectral and analytical data. This solid showed sharp bands at 1750, 1698, 3395, 1612, and 1276 cm$^{-1}$ corresponding to C=O, C=O, N-H, C=N and C=S respectively in its IR spectrum. The $^1$H NMR spectrum (DMSO-d6) of this solid showed broad singlet at 1.78 δ for six proton of three –CH$_2$ group of piperidine nucleus. The broad singlet appeared at 3.32 δ corresponded to two proton of -NH$_2$ group. The singlet at 3.84 δ for four proton of two –CH$_2$ group of piperidine ring and singlet at 6.29 δ for one proton of N=C-H group. The multiplet appeared at 7.20-8.12 δ corresponded to five aromatic proton of benzene ring and a broad singlet at 11.40 δ corresponding to a proton of N-H group. The mass spectrum of this solid showed characteristic M$^+$ peak at 391 and M$^{+2}$ at 393 due to Chlorine. (Exact mass is 391.09) and
corresponded to the molecular formula $\text{C}_{17}\text{H}_{18}\text{ClN}_5\text{O}_2\text{S}$. On the basis of these analysis structure 5a was assigned to this solid i.e., 1-(4-chlorophenyl)-(2, 5-dihydro-2, 5-dioxo-1-phenyl-4-(piperidin-1-yl)-1H-pyrrol-3-yl)-ethylene)-thiosemicarbazide.

$\text{H NMR Spectra of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrol-3-yl)methylene} $ \text{semicarbazide, 5a}$

$\text{C NMR Spectra of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrol-3-yl)methylene} $ \text{semicarbazide, 5a}$
Spectral Data

Synthesis of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrole-3-carbaldehyde, 4a

M.P. 180-182 °C, Yield (%): 86, (1.60 g), Colour: Yellow Solid

IR (KBr) (v): 2856, 2754, 1751, 1709, 1660 cm⁻¹; ¹H NMR (CDCl₃) δ: 1.84 (S, 6H, 3 x CH₂), 4.10 (S, 2H, 2 x CH₂), 4.38 (S, 2H, 2 x CH₂), 7.25-7.45 (m, 4H, Ar-H), 9.76 (S, 1H, CHO); ¹³C NMR (CDCl₃) δ: 23.8, 27.4, 29.5, 51.09, 57.77, 97.18, 127.71 (2C’S), 129.23 (2c’S), 129.42, 133.91, 148.06, 169.51, 182.12. MS (m/z, %): 319 [M⁺] and 320 [M⁺²]. Analysis Calculated for C₁₆H₁₅ClN₂O₃ Calcd: C(60.29), H(4.74), N(8.79), Found: C(60.00), H(5.07), N(9.11)

Synthesis of 1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1H-pyrrole-3-carbaldehyde- 4b

M.P. 178-180 °C, Yield (%): 78, (1.50 g), Colour: Golden Yellow Solid

IR (KBr) (v): 2880, 2795, 1765, 1709, 1670 cm⁻¹; ¹H NMR (CDCl₃) δ: 3.80 (S, 4H, 2 x CH₂), 4.20 (S, 2H, CH₂), 4.48 (S, 2H, CH₂), 7.30-7.50 (m, 4H, Ar-H), 9.75 (S, 1H, CHO); ¹³C NMR (CDCl₃) δ: 49.3, 56.6, 66.8, 67.3, 98.20, 126.3(2C’S), 128.1,128.8, (2C’S), 130.3, 148.3, 162.8, 169.8, 182.30 MS (m/z, %): 321 [M⁺] and 322 [M⁺²] Analysis Calculated for C₁₅H₁₃ClN₂O₄ Calcd: C(56.17), H(4.09), N(8.73), Found: C(55.88), H(4.34), N(9.12)

Synthesis of 1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-1-phenyl-4-(pyrrolidin-1-yl)-1H-pyrrole-3-carbaldehyde- 4c

M.P. 162-164 °C, Yield(%): 84, (1.50g), Colour: Fresh Yellow Solid

IR (KBr) (v): 2865, 2783, 1768, 1706, 1665 cm⁻¹; ¹H NMR (CDCl₃) δ: 2.18 (m, 4H, 2 x CH₂), 4.25 (m, 4H, 2 x CH₂),7.32-7.60 (m, 4H, Ar-H), 9.86 (S, 1H, CHO); ¹³C NMR (CDCl₃) δ: 21.18, 25.12(2C’S), 99.8, 127.10 (2C’S), 126.00, 126.40(2c’S), 129.4 (2C’S), 137.33, 142.8, 166.8, 183.7 MS (m/z, %): 305 [M⁺] and 306 [M⁺²] Analysis Calculated for C₁₅H₁₃ClN₂O₃ Calcd: C(59.12), H(4.09), N(9.19) Found: C(58.86), H(4.34), N (9.48)

Synthesis of 1-((1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(piperidin-1-yl)-1H-pyrrol-3-yl)methylene)thiosemicarbazide- 5a

M.P. 168-170 °C Yield(%): 82, (1.58g), Colour: Orange Solid IR (KBr) (v): 1751, 1696, 3388, 1615, 1275cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 1.66 (bs, 6H, 3 x CH₂), 3.40 (s, 2H, CH₂), 3.83(s, 2H, CH₂), 7.11(S, 1H, =C-H), 7.38-7.53 (dd, 4H, Ar-H), 8.18(s, 2H, NH₂),
11.41 (bs, 1H, N-H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta$: 23.80 (2C'S), 27.39, 27.71, 29.70, 51.09, 57.77, 97.85, 127.71 (2C'S), 129.23 (2C'S), 129.63, 133.91, 148.06, 160.2, 163.40 169.51, 180.12 ppm; MS (m/z %): 391[M$^+$] and 393[M$^{+2}$]

**Analysis Calculated for C$_{17}$H$_{18}$ClN$_5$O$_2$S:**
Calcd: C(52.10), H(4.63), N(17.78); Found: C(51.83), H(5.14), N(17.04)

**Synthesis of 1-(1-(4-chlorophenyl)-2,5-dihydro-4-morpholino-2,5-dioxo-1H-pyrrol-3-yl)methylene)thiosemicarbazide- 5b**

M.P. 158-160 °C, Yield(%): 90, (1.64g), Colour: Orange Solid IR (KBr) (v): 7175, 1699, 3385, 1610, 1276 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$: 3.75 (bs, 4H, 2 x CH$_2$), 4.20 (s, 2H, CH$_2$), 4.30 (s, 2H, NH$_2$), 6.72 (s, 1H, =C-H), 7.24-8.10 (m, 4H, Ar-H), 11.20 (bs, 1H, N-H) ppm; $^{13}$C NMR ( CDCl$_3$) $\delta$: 23.90 (2C'S), 27.58, 27.95, 29.95, 61.15, 98.28 127.80 (2C'S), 129.80 (2C'S), 129.95, 133.75, 153.20, 162.5, 163.38, 168.67, 180.56 ppm; MS (70 eV) m/z (%): 391[M$^+$] and 393[M$^{+2}$] Analysis Calculated for C$_{16}$H$_{16}$ClN$_5$O$_2$S : Calcd: C(48.79), H(4.09), N(17.78); Found: C(48.53), H(4.37), N(18.05)

**Synthesis of 1-((1-(4-chlorophenyl)-2,5-dihydro-2,5-dioxo-4-(pyrrolidin-1-yl)-1H-pyrrol-3-yl)methylene)thiosemicarbazide- 5c**

M.P. 181-183 °C, Yield(%): 88, (1.57g), Colour: Orange Solid IR (KBr) (v): 7175, 1699, 3385, 1606, 1276 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$: 1.88 (s, 4H, 2 x CH$_2$), 2.20 (s, 2H, CH$_2$), 2.80 (s, 2H, CH$_2$), 3.83 (s, 2H, NH$_2$), 7.10 (s, 1H, =C-H), 7.30-8.10 (m, 4H, Ar-H), 11.40 (bs, 1H, N-H) ppm; $^{13}$C NMR ( CDCl$_3$) $\delta$: 24.6 (2C'S), 52.3, 54.20, 118.2, 122.5, 127.6 (2C'S), 129.5 (2C'S), 130.3, 140.2, 161.7, 165.3, 168.5, 181.7 ppm; MS (m/z %): 362[M$^+$] and 363 [M$^{+2}$] Analysis Calculated for C$_{16}$H$_{16}$ClN$_5$O$_2$S : Calcd: C(50.86), H(4.27), N(18.53); Found: C(48.53), H(4.56), N(18.85)

**CONCLUSION**

Here we described the synthesis of thiosemicarbazide derivatives of 1-chlorophenyl-4-dialkylamino-3-carbaldehyde-N-arylmaleimides 4a-c by nucleophilic condensation of trans-3,4-dibromo-1-(4-chlorophenyl)pyrrolidine-2,5-dione.1-1-chlorophenyl-4-dialkylamino-3-carbaldehyde-N-arylmaleimides 4a-c were reacting with thiosemicarbazide to obtained thiosemicarbazone 5a-c with good yield. All these synthesized compounds are well characterized by spectral and analytical method and are new addition to the family of heterocyclic compounds. Further it can be a good source for future researcher to develop new potent bioactive Thiosemicarbazide derivatives.
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