Synthesis and Characterization of Novel Semicarbazide Derivative of Disubstituted *N, N*-Dimethylaminomaleimides

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Abstract

The compound 1 was reacted with bromine in DMF to obtaindibromosuccinimide2.The compound 2 was reacted with *N, N* –dimethyl amine as a base followed de hydro halogenation to obtain3-bromo-1-(4-chlorophenyl)-1H-pyrrole-2,5-dione as intermediate compound further on Vilsmeier Haack formylation afforded compound 4with good yield. The condensation of 1- (4-halophenyl) -4 -(dimethylamino) -2, 5-dihydro-2, 5-dioxo-1H –pyrrole -3- carbaldehyde 4a-bwith semicarbazide hydrochloride in ethanol in presence of acetic acid furnished compound 5a-bwith 83% yield. All the synthesized compounds were well characterized by spectral and analytical data.

Keywords: Maleimide, *N,N*-dimethylamine, VilsmeierHaack formylation, enaminone intermediateand Semicarbazone.

Introduction:

Maleimides shows a widerange of biological activities such as antibacterial [1-2] and antifungal [3], antiprotozoal [4],antiangiogenic [5], analgesic [6], antitress agents [7], cytotoxic, DNA binding and apoptoticinducing activity.[8] A biological property of these compounds includes angiogenesisinhibition[9], protein kinase inhibition [10], ant proliferative activity [11], and antimicrobial [12]and antifungal[13] properties.

Semicarbazone derivatives are prepared via the reaction of aldehydes or ketones with semicarbazide hydrochloride in the presence of an acid or a base as catalyst [14-15]. Semicarbazone were found to posses various pharmacological properties such as antimicrobial [16-17], anti-inflammatory [18] anticonvulsant [19-20], antioxidant [21] antiepileptic [22], and antiproliferative [23] activities. These are useful for the protection, purification and characterization of carbonyl compounds [24] and also act as intermediate for the synthesis of biologically important heterocyclic moieties. The literature survey revealed that semicarbazones had been acompound with broad range of activities including anticonvulsant, antitubercular, anticancerand antimicrobial activity[25].

Material and Methods

Melting points were determined on a Gallenkamp melting point apparatus, Mod.MFB-595 in open capillary tube and are uncorrected. FT-IR spectra were recorded on Schimadzu FTIR-408 instrument in KBr pellets. ^{1}H and ^{13}C spectra were recorded on Bruker Avance II (500MHz) spectrometer in

$CDCl_3$and DMSO. Chemical shifts are reported in ppm with respect to tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out on Hosli CHN analyzer and are within ± 0.4 of theoretical percentages. The progress of the reaction was monitored by thin layer chromatography (TLC, 0.2 mm silica gel 60 F_{254} ,Merck plates) and visualized using UV light(254 and 366 nm) for detection. All commercial grade chemicals were purchased from S.D. Fine chemicals India and used without further purification while solvents were purified by standard literature procedures.

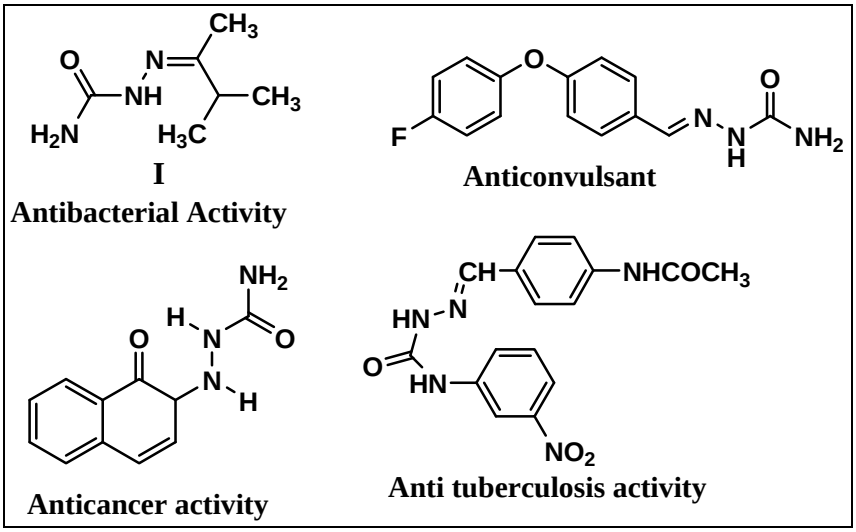


Figure 1 Synthesis of 1-(4-halophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde 4a-b

Experimental:

General procedure for synthesis of (4a-c):

1-(4-halophenyl)-1H-pyrrole-2,5-dione, **1a-b**(0.01 mol) in DMF (8 mL) was vigorously stirred at room temp. The mixture of bromine (0.011 mol) in DMF was added drop wise at 25^0C and stirred for 1-2.5 hrs.with constant stirring, white solid separated was then filtered,washed with cold water, dried and recrystallized usingethanol to obtain compound **2** [26].

To a solution of trans-3, 4-dibromo-1-(4-halophenyl) pyrrolidine-2,5-dione**,2** (0.01 mol) in DMF (10 mL), N,N-dimethylamine(0.03 mol) wasadded drop wise at 10^0C and stirred for 30min. The reactionmixture was poured over crushed ice. The golden yellow solidseparated out was filtered and recrystallized from aqueous ethanol to obtained compound **3a-b**respectively.[26]

Synthesis of 1-(4-chlorophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione, 3a

M.P(^{o}C).:97-98, Yield (%):84, Colour:Yellow solid

IR (KBr) (ν):1740, 1693, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:3.61 (S, 6H, 2 x CH_3), 5.99 (S, 1H), 7.25-7.50 (m, 4H, Ar-H); MS (m/z ,%): 250 [M^+], 252 [M^{+2}], Analysis Calculated for $C_{12}H_{11}ClN_2O_2$ Calcd:C(57.49), H(4.42), N(11.17), Found:C(57.21), H(4.60), N(11.28)

Synthesis of 1-(4-bromophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione, 3b

M.P(^{o}C).:104-105, Yield (%):81, Colour:Yellow solid

IR (KBr) (ν):1748, 1692, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:3.67 (S, 6H, 2 x CH_3), 6.08 (S, 1H), 7.20-7.52 (m, 4H, Ar-H); MS (m/z ,%): 294 [M^{+}], 296 [M^{+2}], Analysis Calculated for $C_{12}H_{11}BrN_2O_2$ Calcd:C(48.84), H(3.76), N(9.49), Found:C(48.63), H(3.98), N(9.60)

VilsmeierHaack adduct prepared from DMF (0.012 mol)and $POCl_3$ (0.05 mol) at 0 ^{0}C was added to a solution of **3a-b** (0.01 mol)in 2 mL DMF, reaction mixture was then stirred at 0-5 ^{0}C for30 min. The reaction mixture was poured into cold water. The yellow product separated on neutralization with aqueous $NaHCO_3$solution was filtered, washed with cold water, dried and purified by column chromatography, to obtained compound **4 a-b**

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

M.P(^{o}C).:181-182, Yield (%):83, Colour:Yellow solid

IR (KBr) (ν):2856, 2754, 1751, 1709, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:3.84 (S, 6H,2 x CH_3), 7.25-7.45 (m, 4H, Ar-H), 9.76 (S, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ:42.50, 48.4, 57.77, 97.18, 127.71 (2C' S), 129.23 (2c'S), 133.91, 148.06, 163.58, 169.51, 182.12, MS (m/z ,%): 278[M^{+}] and 280 [M^{+2}], Analysis Calculated for $C_{13}H_{11}ClN_2O_3$ Calcd:C(56.03), H(3.98), N(10.05), Found:C(55.84), H(4.21), N(11.18)

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

M.P(^{o}C).:196-197, Yield (%):78, Colour:Yellow solid

IR (KBr) (ν):2878, 2780, 1780, 1727, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ:3.73(S, 6H,2 x CH_3), 7.20-7.50 (m, 4H, Ar-H), 9.81 (S, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ:42.60, 48.70, 58.73, 98.16, 126.70 (2C' S), 129.63 (2c'S), 133.90, 148.20, 163.45, 169.58, 182.10, MS (m/z ,%):322[M^{+}] and 324 [M^{+2}];Analysis Calculated for $C_{13}H_{11}BrN_2O_3$ Calcd:C(48.32), H(3.43), N(8.67), Found:C(48.08), H(3.63), N(8.86)

General procedure for synthesis of (5a-c):

The compound **4a-c** (0.01 mol)in ethanol (10 mL), catalytic amount of acetic acid was added. The reaction mixture was stirred for 20 min. till we get clear solution. To this mixture semicarbazide hydrochloride solution (0.01 mol) was added while stirring. The temperature of reaction mixture was maintained at 50^{0}C for 20 min. The orange solid separate out, the solid separated was collected and then filtered to afford compounds **5a-c** respectively.

Synthesis of1-((1-(4-chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)methylene)semicarbazide, 5a

M.P(^{o}C).:188-189;Yield (%):77;Colour:Orange solid

IR (KBr) (ν):1751, 1696, 3388, 1615, 1275cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d^{6}) δ:3.73 (S, 6H, 2 x CH_3), 7.11(S, 1H, =C-H),7.38-7.53 (dd, 4H, Ar-H), 8.18 (s, 2H, NH_2), 11.41 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ:46.56 ,51.09, 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%)**:** 335 [M^{+}] and 337 [M^{+2}];Analysis Calculated for $C_{14}H_{14}ClN_5O_3$: Calcd: C(50.08), H(4.20), N(20.86); Found:C(49.86), H(4.43), N(21.03)

Synthesis of1-((1-(4-bromophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)methylene)semicarbazide, 5b

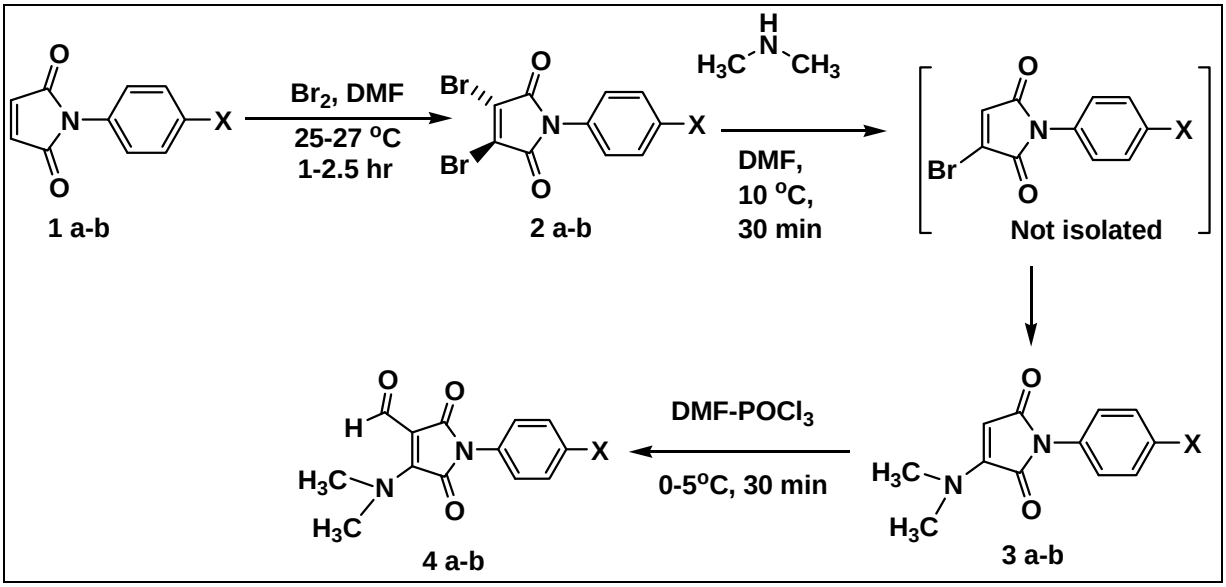
M.P(°C).:203-204;Yield (%):84, Colour:Orange solid

IR (KBr) (ν):1765, 1690, 3385, 1638, 1280 cm^{-1}; ^1H NMR (500 MHz, DMSO-d^6) δ:3.64 (S, 6H, 2 x CH_3), 7.10(S, 1H, =C-H),7.21-7.50 (dd, 4H, Ar-H), 8.21 (s, 2H, NH_2), 11.40 (bs, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ:44.50 ,57.06, 97.15, 127.70 (2C'S),129.20(2C'S), 128.60, 133.95, 148.23, 160.28, 163.60 169.67,181.10 ppm; MS (m/z%**):** 379 [M^+] and 381 [M^{+2}] Analysis Calculated for $C_{14}H_{14}BrN_5O_3$: Calcd: C(44.23), H(3.71), N(18.42); Found:C(44.01), H(3.98), N(18.64)

Results and discussion:

The compound **1a-b**were reacted with bromine in DMF at 25-27 °C for 1- 2.5 hr to obtain 3,4-dibromo-1-(4-halophenyl)-1H-pyrrole-2,5-diones **2a-b.** The compound **2**wasreacted with *N,N*-dimethylamine as a base followed dehydrohalogenationafforded1-(4-halophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione**3.**Installation of an amino functionality at C-3 position in **3a-b** should increase nucleophilicity at C-4 position. 1-(4-halophenyl)-3-(dimethylamino)-1H-pyrrole-2,5-dione**3** was reacted with bromine in DMF at 0°Cfor 5 min afforded compound **4a-b**. VilsmeierHaackformylation of **3a-c** at 0-5°C afforded compound 1-(4-halophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehydes **4a-b**with good yield.**(Scheme-1)**

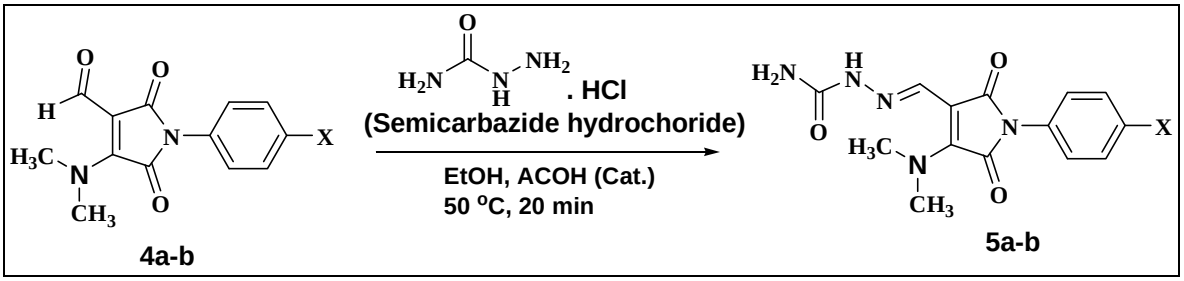
Further condensation of 1-(4-halophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde**4a-b**with semicarbazide hydrochloride in ethanol in presence of acetic acid at50°C furnished orange color solid compound (1E)-1-((1-(4-chlorophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl)methylene)semicarbazide**5** with 84% yield. [27]All the synthesized compounds were well characterized by Spectral and analytical techniques.



1 to 4	a	b
X	Cl	Br

Scheme 1

Synthesis of semicarbazide derivatives of 4-dialkylamino-3-carbaldehyde-*N*,*N* dimethylamino maleimides5a-b



4, 5	a	b
X	Cl	Br

Scheme2

The IR spectra of **4a** showed the characteristics conjugated aldehyde carbonyl stretching frequency at 1705-1708 cm^{-1}, (C-Cl) stretching at 1615-1627cm^{-1} and **(**H-C=O) at 2780-2792 cm^{-1} The ^{1}H NMR spectrum ($CDCl_3$) of this solid showed broad singlet at 3.80δ for six proton of twomethyl group. The multiplets appeared at 7.20-7.50 δ corresponded to four aromatic proton of benzene ring and a broad singlet at 9.71 δ corresponding to a proton of H-C=O group. The ^{13}C NMR spectrum ($CDCl_3$) of this solid showed signal at 40.5 and 50.7 δ corresponds to the carbon of two methyl group. The aromatic carbon appears at their respective position. The signal appeared at 163.58 and 169.51 δ corresponded to two carbonyl carbon of amide group. The signal appeared at 182.12 δ corresponded to carbonyl carbon of aldehyde.

The compound obtained was characterized by spectral and analytical data. This solid showed sharp bands at 1751, 1696, 3388 & 1615 corresponding to C=O, C=O, N-H & C=N respectively in its IR spectrum. The ^{1}H NMR spectrum (DMSO-d6) of this solid showed broad singlet at 3.66 δ for six proton of twomethyl group. The broad singlet appeared at 3.40 δ corresponded to two proton of -N**H**$_2$ group. The singlet at 7.11 δ for one proton of N=C-**H** group and singlet appeared at 8.18 corresponded to two proton of -NH_2 group.The doublets appeared at 7.38 δ and 7.53 δ corresponded to four aromatic proton of benzene ring and a broad singlet at 11.41 δ corresponded to a proton of N-**H** group. The ^{13}C NMRspectrum (DMSO-d6) of this solid showed signal at 43.70 and 51.40 δ corresponds to the two carbon of methyl group. The aromatic carbon appears at their respective position. The signal appeared at 163.60 and 169.55 δ corresponded to two carbonyl carbon of amide group. The peak appears at 176.10 δ corresponded to carbonyl carbon of oxamide.

Conclusion:

Herein we synthesized novel semicarbazone derivatives of disubstituted *N*,*N*-dimethylamine-maleimides with 84 % yield.. The main advantage of our method are clean, easy operational & simplicity of reaction. Here we described the synthesis of semicarbazide derivatives of 1-(4-halophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde **4a-b** by nucleophilic condensation of trans-3,4-dibromo-1-(4-halophenyl)pyrrolidine-2,5-dione,**3 a-b**with semicarbazide hydrochloride. 1-(4-halophenyl)-4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrole-3-carbaldehyde **4a-b**were reacting

with semicarbazide hydrochloride to obtained semicarbazone **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.

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