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A convenient one pot preparation of 4-thiazolidinones from enaminolactones

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Abstract: Enaminones **3** and **4**, precursors of 4-thiazolidinones, were prepared by condensing tetronic acid (**1a**) and 4-hydroxy 6-methyl pyrone (**1b**) respectively with thiosemicarbazide derivatives **2** in refluxing ethanol. The 4-thiazolidinones **6**, **7** derivatives were obtained by reacting compounds **3** or **4** with ethyl 2- bromo propionate **5** in the presence of anhydrous sodium acetate in ethalonic medium. Similarly, **9** products were synthesized by action of benzyl 2-bromo acetate **8** on **3**.

Keywords: Pyrones; tetronic acid; thiosemicarbazides, enaminones; thiazolidinones.

1. Introduction

The structures of 4-thiazolidinones and 4-imino thiazolidinones are widely studied for their pharmacological properties.[1-2] The 4-thiazolidinone derivatives are known to possess anti-mycobacterial[3-4], anti-fungal[5], anti-tuberculosis[3,6-7], anti-convulsant[8], anti-inflammatory[9-11] and anti-HIV[12-14] activities. Various synthetic approaches of these molecules were reported.[2,3,9,11,12,15-20] Nevertheless a common synthetic strategy to construct imino thiazolidinones is the cyclization of thiourea or thiosemicarbazide derivatives with α-halo esters or thioglycolic acids in presence of inorganic base (i.e., NaOAc) in polar solvents using either a conventional [3,11-16] or microwave irradiation methods.[21-23]

In this paper, we are interested in the construction of this heterocylic ring system from tetronic acid (n=0, **1a**) and 4-hydroxy 6-methyl 2-one-pyran (n=1, **1b)** with thiosemicarbazide derivatives **2** which give enaminones **3** and **4** respectively. These reacted with 2-bromo propionate **5** or benzyl 2-bromo acetate **8** leading to 4-thiazolidinones **6**, **7** and **9** respectively.

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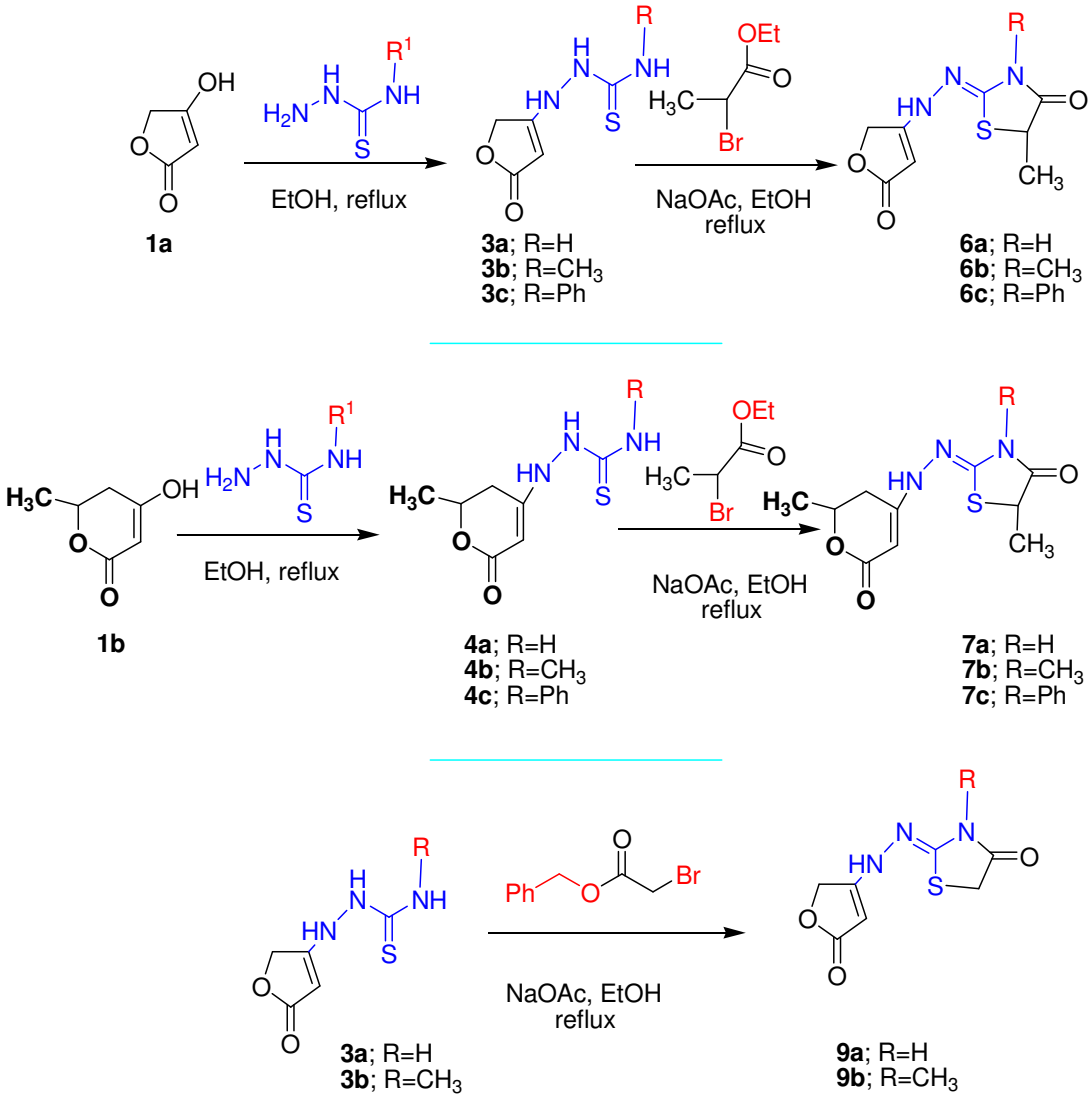
Preparation of 4-thiazolidinones from enaminolactones

Scheme 1 summarizes the chemical strategy used for the preparation of these compounds**.**

2. Results and Discussion

The synthesis of enaminolactones **3**, **4** was carried out, in good yields as previously reported[24], by reacting a suitable tetronic acid (**1a**) or 4-hydroxy-6-methyl pyrane (**1b**) with an appropriate substituted thiosemicarbazide **2** in ethanol at reflux.



Scheme 1. Synthesis of 4-thiazolidinone structures.

Reaction of intermediates **3** and **4** with ethyl 2- bromo propionate **5** or benzyl 2-bromo acetate **8** as cyclising reagents, in boiling absolute ethanol containing 3 equimolars of anhydrous sodium acetate and acetic acid as catalyst, afforded the 4- thiazolidinones **6**, **7** and **9** which were purified on chromatography column (Scheme 1; Table 1).

Enaminolactone thiosemicarbazid group **3** and **4** contains four nucleophilic centers, i.e. N_a, N_b, N_c and the sulphur atom. Cyclisation possibilities of compounds **3** or **4** with ethyl 2- bromo propionate

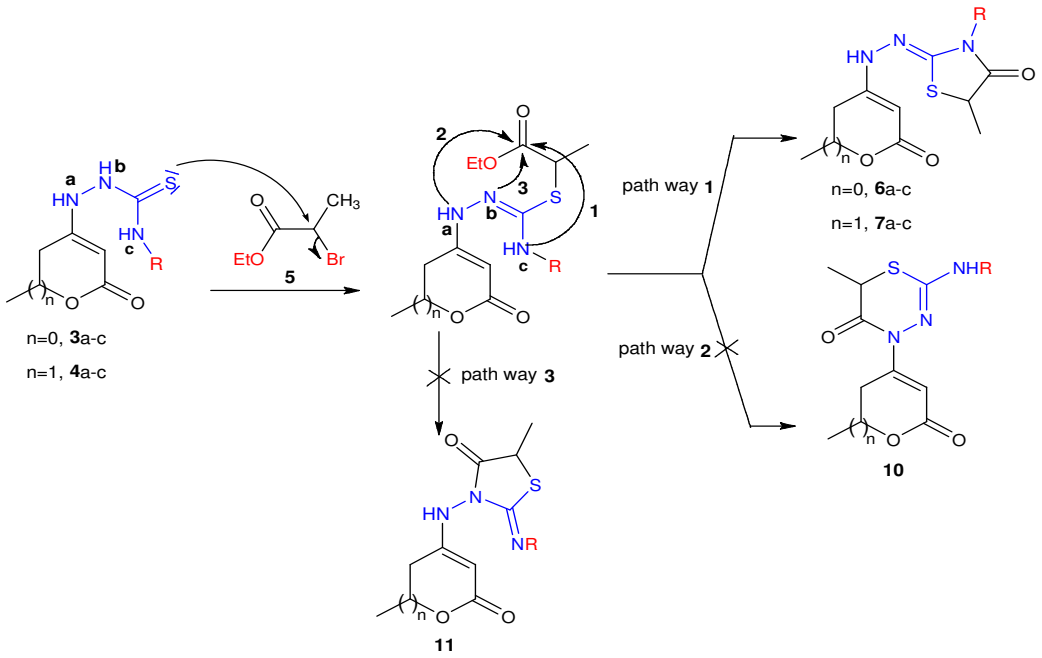
5 could be achieved either by: nitrogen N_a with sulphur (path way 1) or N_b with sulphur (path way 2) or N_c with sulphur (path way 3) to lead to **6**, **7** and **10** or **11** structure respectively. It should be noted that cyclisation reaction of **3** or **4** with ethyl 2- bromo propionate **5** to **10** would not promote due to the N_a free-double bound engaged in a conjugated ring system[2], that makes this atom less nucleophilic in comparison with N_b and N_c atoms.

In the used operating conditions, sodium acetate captures the nitrogen proton N_b and results in thiol form[2], allowing the interaction type Soft-Soft between sulphur atom and the electrophile center (CH-Br) according to Pearson's HSAB (Hard and Soft acids and bases) rules[25-26]. The interaction Hard-Hard of nitrogen N_c with the carbonyl function leads to 4- thiazolidinones **6**, **7** and excluses the formation of structures **11**.

Therefore, the cyclization reaction might be summarised in two steps:

First, the reaction is thought to be an S-alkylation of compounds **3** and **4** in its thiol form (due to the sodium acetate used).

The second step involves the ethanol removal and regeneration of acetic acid to give 4-thiazolidinones.



Scheme 2. Mechanism reaction of 4-thiazolidinones **6** and **7** from enaminolactones and ethyl 2- bromo propionate

Compounds **9** were obtained with a similar reaction mechanism using benzyl 2-bromo acetate **8** as reagent. Both analytical and spectral data of all the synthesized compounds are in full agreement with the formation of 4-thiazolidinones structures **6** and **7**.

The IR spectra of 4- thiazolidinones **6**, **7** and **9** gave lactam (C=O) stretching bands of the thiazolidinones ring at 1700-1705 cm^{-1} in addition to the bands stretching (C=O) at 1651 and 1650 cm^{-1} of enaminolactones**.**

The ^{1}H-NMR spectra of these 4-thiazolidinone derivatives, reveal the absence of N_C-H and N_b-H of enaminolactones **3** or **4** commonly observed at 9-10 ppm and the presence of two new signals at 1.52 ppm as a doublet (J= 9 Hz) and 4.50 ppm as a quadruplet (J=9Hz) attributed respectively to the methyl group -C<u>H</u>$_3$ and SC<u>H</u>CO proton of thiazolidinone moiety in structures **6** and **7.** On the other

hand, peaks at 19, 158 and 176 ppm in the ^{13}C-NMR spectrum of structures **6a-c** and **7a-c** are assigned to the methyl group -$\underline{C}H_3$, the imine C=N and carbonyl $\underline{C}$=O functions respectively.

In conclusion, a series of 4-thiazolidinones **6**, **7** were synthesized from enaminolactones **3** or **4** and ethyl 2- bromo propionate **5** in the presence of anhydrous sodium acetate and acetic acid in refluxing absolute ethanol. Similarly, these enaminolactones react with benzyl 2-bromo acetate **8** to lead **9** derivatives. The reaction mechanism of these molecules shows a regiospecific cyclisation, involving the N_c nitrogen and the sulphur atom.

3. Experimental

(Melting points were measured on a Buchi 512 apparatus and were uncorrected. FTIR were taken in Nujol on a Perkin –Elmer spectrometer. The ^{1}H NMR spectra (250 MHz) and ^{13}C NMR (63 MHz) were run on a Bruker spectrometer in DMSO- d_6 or $CDCl_3$ using tetramethyl silane as internal standard. The impact ionisation (IE) mass spectra were recorded on a Nermag R-10-10C at 70 ev. The elemental analysis data were performed on a Thermo Electron Flash EA 1112. Chemicals were purchased from Aldrich and Fluka.

The preparation of enamine derivatives **3** and **4** were previously described by us.[24]

3.1. General procedure for the formation of 4-thiazolidinones 6a-c and 7a-c.

10 mL of appropriate thiosemicarbazide **3** or **4** and 12 mL of ethyl bromo propionate **5** were refluxed in 30 mL for 8-9 hours of absolute ethanol in the presence of 4 mL of anhydrous sodium acetate and 10 drops of acetic acid.

The reaction mixture was cooled and concentrated under reduced pressure. Then, 30 mL of water was added to the residue and was extracted with 40 mL of ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4. The product was isolated and separated on chromatography column employing different eluants (**7a**-**c**: CH_2Cl_2/ ethyl acetate (7:3); **6a**: petroleum ether / CH_2Cl_2 (5:1); **6b**: CH_2Cl_2/ ethyl acetate (9:1); **6c**: ethyl acetate).

Py: pyrone; Th: thiazolidinone.

5-methyl-1,3-thiazolidine-2,4-dione 2-[(5-oxo-2,5-dihydrofuran-3-yl)hydrazone] (6a):
Yield: 30 %; yellow crystal**;** m.p. 110-112 ^{o}C**.** IR (Nujol, cm^{-1}) 1650 (C=O_{pyr}), 1701 (C=0_{Th}); ^{1}H NMR (250 MHz, DMSO- d_6) (δ/ppm): 1.52 (d, 3H, Th, CH_3 *J*= 9 Hz), 4.33 (q, 1H, Th, CH, J=9Hz), 4.67 (s, 1H, py =CH), 4.74 (s, 2H, py CH_2), 9.78 (s, 1H, NH_a), 11.72 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 19.78 (CH_3), 45.13 (CH), 67.16 (CH_2), 81.93 (=CH), 158.61 (N=C), 167.06 (NC=), 175.05 (OC=O), 176.30 (NC=O). MS. (IE, 70eV): m/z 227([M+.], 22%), 183(33), 129(60), 100(15), 85(100), 83(23). Anal. Calcd. for $C_8H_9N_3O_3S$: C, 42.28; H, 3.99, N, 18.49; O, 21.12; S, 14.11. Found: C, 42.40; H, 3.85, N, 18.30.

3,5-dimethyl-1,3-thiazolidine-2,4-dione 2-[(5-oxo-2,5-dihydrofuran-3-yl)hydrazone] (6b):
Yield: 68 %; Yellow crystal**;** m.p. 200-202 ^{o}C**.** IR (Nujol, cm^{-1}) 1651 (C=O_{pyr}), 1702 (C=0_{Th}); ^{1}H NMR (250 MHz, DMSO- d_6) (δ/ppm): 1.55 (d, 3H, Th, CH_3, *J*= 9 Hz), 3.06 (s, 3H, NCH_3), 4.38 (q, 1H, Th, CH, J=9Hz), 4.79 (s, 1H, py =CH), 4.81 (s, 2H, py CH_2), 10.17 (s, 1H, NH_a); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 19.75 (CH_3), 31.25 (CH_3), 45.16 (CH), 67.20 (CH_2), 81.95 (=CH), 158.63 (N=C), 167.10 (NC=), 175.07 (OC=O), 176.35 (NC=O). S.M (IE, 70eV): m/z 241([M+.], 18%), 143(31), 197(79), 104(35), 99(10), 83(100). Anal. Calcd. for $C_9H_{11}N_3O_3S$: C, 44.80; H, 4.60; N,17.42; O, 19.89; S,13.29. Found: C, 44.60; H, 4.80; N, 17.40.

5-methyl-3-phenyl-1,3-thiazolidine-2,4-dione-2-[(5-oxo-2,5-dihydrofuran-3-yl) hydrazone] (6c): Yield: 33 %; Yellow crystal; m.p. 220-222 °C**.** IR (Nujol, cm^{-1}) 1650 ($C=O_{pyr}$), 1700 ($C=0_{Th}$); ^1H NMR (250 MHz, DMSO- d_6) (δ/ppm):1.66 (d, 3H, Th, CH_3, *J*= 9 Hz), 4.48 (q, 1H, Th, CH, J=9Hz), 4.58 (s, 1H, py =CH), 4.63 (s, 2H, py CH_2), 7.34-7.51 (m, $5H_{aro}$), 10.18 (s, 1H, NH_a); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 19.87 (CH_3), 44.11 (CH), 67.02 (CH_2), 82.45 (=CH), 129.07, 129.52, 129.81, 135.71 (C_{aro}), 158.61 (N=C), 167.13 (NC=), 174.33 (OC=O), 174.85 (NC=O). S.M (IE, 70eV): m/z 303 ([M+.], 7%), 205(100), 129(34), 100(5), 85(81), 83(10). Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85; O, 15.82; S, 10.57. Found: C, 55.60; H, 4.28; N, 13.97.

5-methyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2*H*-pyran-4-yl) hydrazone] (7a): Yield: 34 %; Yellow crystal; m.p. 195-197 °C. IR (Nujol, cm^{-1}) 1650 ($C=O_{pyr}$), 1702 ($C=0_{Th}$); ^1H NMR (250 MHz, DMSO- d_6) (δ/ppm): 1.44 (d, 3H, py, CH_3 *J*= 8 Hz), 1.65 (d, 3H, Th, CH_3, *J*= 9 Hz), 2.58-2.85, (m, 2H, py CH_2), 4.26 (m, 1H, py CH), 4.52 (q, 1H, Th, CH, J=9Hz), 4.88 (s, 1H, py =CH), 9.50 (s, l, 1H, NH_a), 11.92 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 19.14 (CH_3), 20.78 (CH_3), 31.84 (CH_2), 44.29 (CH), 71.80 (CH), 83.35 (=CH), 158.0 (N=C), 167.24 (NC=), 176.17 (OC=O), 177.10 (NC=O). S.M (IE, 70eV): m/z 255([M+.], 14%), 211(40), 131(100), 112(55), 102(23), 87(24). Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H,5.13; N,16.46 ; O,18.80; S, 12.56. Found: C, 42.50; H, 3.91, N, 18.32.

3,5-dimethyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2*H*-pyran-4-yl)hydrazone] (7b): Yield: 30 %; Light brown oil; IR (Nujol, cm^{-1}) 1650 ($C=O_{pyr}$), 1702 ($C=0_{Th}$); ^1H NMR (250 MHz, $CDCl_3$) (δ/ppm): 1.45 (d, 3H, py, CH_3 *J*= 8 Hz), 1.62 (d, 3H, Th, CH_3, *J*= 9 Hz), 2.50-2.65, (m, 2H, py CH_2), 3.44 (s, 3H, NCH_3), 4.19 (m, 1H, py CH), 4.55 (q, 1H, Th, CH, J=9Hz), 4.64 (s, 1H, py =CH), 9.65 (s, l, 1H, NH_a); ^{13}C NMR (63 MHz, $CDCl_3$) (δ/ppm): 19.49 (CH_3), 20.88 (CH_3), 30.16 (NCH_3), 34.69 (CH_2), 45.94 (CH), 73.08 (CH), 83.35 (=CH), 158.42 (N=C), 169.11 (NC=), 175.60 (OC=O), 176.69 (NC=O). S.M (IE, 70eV): m/z 269([M+.], 30%), 145(25), 116(70), 112(100), 101(54), 87(5). Anal. Calcd. for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N,15.60; O, 17.82; S, 11.91. Found: C, 49.25; H, 5.70; N,15.43.

5-methyl-3-phenyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2*H*-pyran-4-yl) hydrazone] (7c): Yield: 32 %; Yellow crystal; m.p. 276-278 °C. IR (Nujol, cm^{-1}) 1652 ($C=O_{pyr}$), 1705 ($C=0_{Th}$); ^1H NMR (250 MHz, DMSO- d_6) (δ/ppm): 1.31 (d, 3H, py, CH_3 *J*= 8 Hz), 1.56 (d, 3H, Th, CH_3, *J*= 9 Hz), 2.50 (m, 2H, py CH_2), 4.58 (m, 1H, py CH), 4.76 (q, 1H, Th, CH, J=9Hz), 4.86 (s, 1H, py =CH), 6.90-7.38 (5H, CH_{ar}); 9.78 (s, l, 1H, NH_a); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 19.53 (CH_3), 21.46 (CH_3), 32.54 (CH_2), 45.04(CH), 72.28 (CH), 83.26 (=CH), 129.01-129.24-129.35-134.40 (C_{aro}), 158.79 (N=C), 168.24 (NC=), 176.97 (OC=O), 177.88 (NC=O). S.M (IE, 70eV): m/z 331([M+.], 30%), 207(25), 178(100), 163(44), 112(54), 87(7). Anal. Calcd. for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; O,14.48; S, 9.68. Found: C, 58.01; H, 5.19; N, 12.60.

3.2. Synthesis of 4-thiazolidinones compounds 9a-b.

A (10 mL) suspension of enaminolactones **3a-b** and 12 mL of benzyl 2-bromo acetate **8** were refluxed in 30 mL of absolute ethanol in the presence 4 mL of anhydrous sodium acetate and 10 drops of acetic acid for 4 hours. The precipitate obtained was filtered and recrystallized in ethanol.

1,3-thiazolidine-2,4-dione 2-[(2-oxo-2,5-dihydrofuran-3-yl)hydrazone] (9a): Yield: 30 %; White crystal; m.p. 230-232 °C**.** IR (Nujol, cm^{-1}) 1651 ($C=O_{pyr}$), 1705 ($C=0_{Th}$); ^1H NMR (250 MHz, DMSO- d_6) (δ/ppm): 4.02 (s, 2H, Th CH_2), 4.67 (s, 1H, py =CH), 4.74 (s, 2H, py CH_2), 9.98 (s, 1H, NH_a), 11.73 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 35.23 (CH_2), 67.16 (CH_2), 81.90 (=CH), 158.60 (N=C), 167.09(NC=), 173.49 (OC=O), 175.06 (NC=O). S.M (IE, 70eV): m/z 213([M+.], 17%), 197(4), 143(100), 117(32), 98(44), 87(12). Anal. Calcd. for $C_7H_7N_3O_3S$: C,39.43; H, 3.31; N, 19.71; O, 22.51; S, 15.04. Found: C, 39.50; H, 3.28; N, 19.68.

3-methyl-1,3-thiazolidine-2,4-dione 2-[(2-oxo-2,5-dihydrofuran-3-yl)hydrazone] (9b): Yield: 40 %; White crystal; m.p. 208-210 ^{o}C; IR (Nujol, cm^{-1}) 1650 (C=O_{pyr}), 1704 (C=0_{th}); ^{1}H NMR (250 MHz, DMSO- d_6) (δ/ppm): 3.10 (s, 3H, NCH_3), 4.00 (s, 2H, Th, CH_2), 4.58 (s, 1H, py =CH), 4.71 (s, 2H, py CH_2), 7.71 (s, 1H, NH_a);_^{13}C NMR (63 MHz, DMSO- d_6) (δ/ppm): 23.56 (NCH_3), 33.95 (CH_2), 67.53 (CH_2), 81.91 (=CH), 158.60 (N=C), 167.10 (NC=), 171.70 (OC=O), 174.06 (NC=O). S.M (IE, 70eV): m/z 227([M+.], 2%), 111(9), 143(65), 131(44), 98(4), 89(100). Anal. Calcd for $C_8H_9N_3O_3S$: C, 42.28; H, 3.99; N, 18.49; O,21.12; S, 14.11. Found: C, 42.30; H, 3.91; N, 18.51.

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