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Synthesis, characterization and antibacterial activity of alkyl, benzyl and chloro substituted benzyl derivatives of nitroketene dithioacetals

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ABSTRACT

Nitromethane (1) upon treatment with Carbon disulfide (2) under ice cold condition in presence of dry methanol / Potassium hydroxide gave dipotassium salt of nitroketene dithioacetal (3). Further treatment of dipotassium salt (3) with alkyl and substituted chloro benzyl bromide furnished bis S,S – alkyl and Substituted chlorobenzyl derivatives (4-10). The structure of the synthesised compounds was characterised using UV, IR, ^{1}H and ^{13}C NMR spectral evidences. The antibacterial activities of products (3-10) were evaluated using Disc-Diffusion method.

Key words: Nitroketene Dithioacetals, S,S- bis alkyl derivatives, S,S-benzyl and substituted chloro benzyl derivatives, dithiaheterocycles, Antibacterial activity.

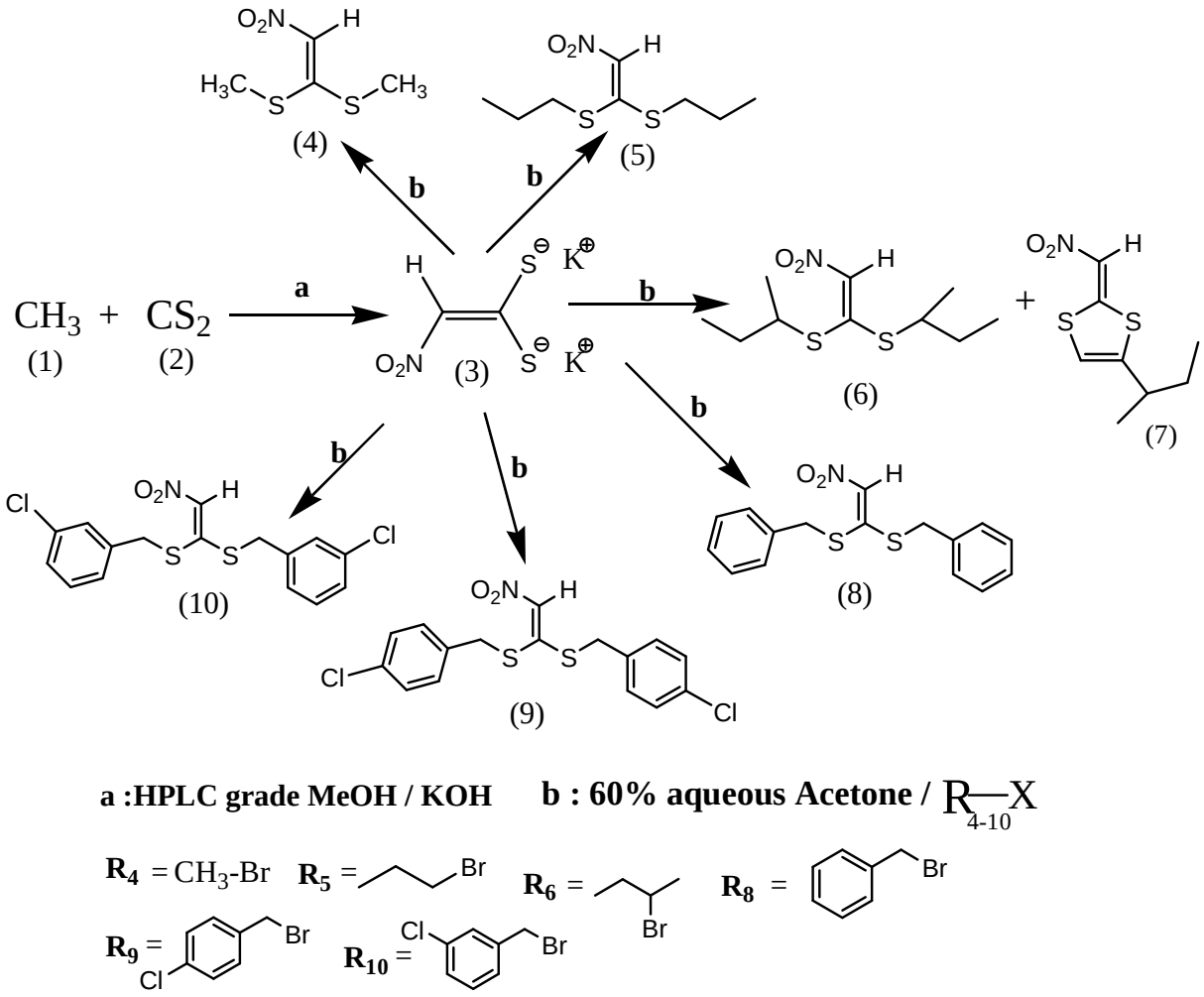
INTRODUCTION

Nitroketene dithioacetals occupy an important role in organo-sulfur chemistry as a two carbon synthon[1-12]. It acts as good Michael acceptors in the synthesis of variety of sulfur heterocycles [1-19]. Recently HSPR et al has reported the synthesis of different bis S-alkylated derivatives of nitroketene dithioacetals by a two step process [1-4]. From the patent literature it is found that sulfoxide derivatives of nitroketene dithioacetals show impressive insecticidal activity[5]. Recently we have reported that the alkyl and aryl group substituted derivatives of nitoketene dithioacetals showed central nervous system depressant activity in albino mice screening animal model experiments [17]. In view of these interesting biological aspects, we became interested to synthesis different alkyl and substituted benzyl derivatives and to study the anti bacterial activity[20] against different Bacteria.

MATERIALS AND METHODS

Analar grade chemicals and reagents were used in all the synthetic steps. The progress of product formation was monitored by TLC using hexane and ethyl acetate solvent system. Purification of all compounds carried out by column chromatography using silica gel 100-200 mesh. IR spectra were recorded in Shimadzu instrument as neat and KBr pellet. ^{1}H & ^{13}C NMR were recorded in Bruker-300 MHz NMR using $CDCl_3$ as solvent.

SYNTHESIS OF CHARCTERISATION OF ALKYL AND SUBSITTUTED BENZYL DERIVATIVES OF NITROKETENE DITHIOACETAL (3-10) (Scheme: I)



Scheme - I Synthesis of Nitroketene dithioacetal derivatives 3-10

Synthesis of Dipotassium salt of 2-nitro-1,1-ethylene dithiolate (3)

To a well stirred and ice cooled solution of carbon disulphide **(2)** (23mL, 0.41mole) and nitromethane **(1)** (18mL, 0.33mole) solution of potassium hydroxide (39g) in 95mL of HPLC grade methanol was added drop by drop for 40 minutes using a pressure equalizing funnel. The stirring was continued for 3hrs at 0^0c to - 5^0c. The reddish brown colour powder formed in the reaction mixture was quickly filtered and washed with dry methanol (3x10mL) followed by dry ether (3x10mL) to yield 38.0g (55.2%) of reddish brown colour powder **(3)**. The salt **(3)** was quickly transferred into brown colour sample bottle to avoid photodecomposition.

General procedure for the synthesis of nitroketene dithioacetal derivatives (4 – 10)

1 gram of dipotassium salt of nitroketene dithioacetal **(3)** (0.0047mole) was taken and well stirred for 5 minutes under rt in 20 mL of 60% aqueous acetone. To the above solution alkyl and substituted benzyl bromide was added drop wise for 10 minutes. The stirring was continued for 12hrs and the product formation was monitored by TLC. The reaction mixture was diluted with ice cold water (35mL) and the formed product was extracted with dichloromethane (35mL). The organic layer was again washed well with brine (20mL) and then dried over anhydrous Na_2SO_4 for 2hrs. Evaporation of the solvent under reduced pressure yielded the yellow colour solid

product **(4)** which on further purified over 100-200 mesh silica gel packed column chromatography using hexane:ethyl acetate (9:1 to 8:2) solvent mixture.

1, 1-di (methylsulfanyl)-2-nitroeth-1-ene (4)
methyl iodide (0.65mL, 0.01mole), Mp: 125^{0}C, Yield: 69% (0.54g) UV (methanol) λmax 356, 294 nm; IR(nujol)ν 3125, 2994, 1513, 1461, 1294, 1256, 918 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 2.53(s, 3H), 7.05 (s, 1H) ppm ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.03, 17.51, 125.21, 163.44ppm.

1, 1-di (propylsulfanyl)-2-nitroeth-1-ene (5)
n-propyl iodide (0.78mL, 0.011mole) , Yield: 63% (0.63g) UV (methanol) λmax 357, 305 nm; IR(nujol) ν 2928, 2828, 1524, 1452, 1309, 1271, 932 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$)δ 1.08 (t, 3H), 1.1 (t, 3H), 1.76 (quintet, 2H), 1.8 (quintet, 2H), 2.94 (t, 2H), 3.01 (t, 2H), 7.06 (s, 1H);ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.35, 13.43, 21.87, 20.67, 36.35, 36.28, 125.16, 162.25 ppm.

1, 1-di [(1-methylpropyl)sulfanyl]-2-nitroeth-1-ene (6)
2-bromobutane (1.28mL, 0.011mole), Yield:21% (0.229g)UV(methanol) λmax 360nm; IR(KBr) ν3124, 2925,1525,1452,630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (q, 6H), 1.43 (quintet, 4H), 1.78 (d, 6H), 3.33 (m, 1H), 3.63 (m, 1H), 7.17 (s, 1H);ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.74, 11.88, 20.13, 21.47, 29.25, 30.37, 43.31, 46.44, 127.24, 161.97ppm.

4-[(1-methylpropyl)sulfanyl]-2-[(E)-1-nitromethylidene]-1,3-dithiole (7)
2-bromobutane (1.28mL, 0.011mole), Yield: 9% (0.109g) UV (methanol) λmax 416 nm; IR (KBr) ν 3060, 2923, 1525, 1458, 617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H), 1.34 (d, 3H), 1.61 (quintet, 2H), 3.15 (m, 1H), 6.96 (s, 1H), 7.71 (s, 1H);ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.72, 21.04, 29.92, 48.12, 121.5, 123.61, 133.5, 167.12 ppm.

1-[(2-nitro-1-[(phenylmethyl)sulfanyl]eth-1-enylsulfanyl)methyl]benzene (8)
benzyl chloride (1.53mL, 0.011mole), Yield: 95% (0.71g) UV (methanol) λmax 358, 304 nm; IR(nujol) ν 3132, 3026, 2927, 1600, 1520, 1446, 1314, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 4.22 (s, 2H), 7.12 (s, 1H) , 7.34 (m, 10H);ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.45, 35.87, 123.14, 125.15, 130.10, 131.18, 134.14, 160.10 ppm.

1-chloro-4-[(4-chlorophenyl)methyl]sulfanyl-2-nitroeth-1-enyl)sulfanyl]methylbenzene (9)
4-Chlorobenzyl chloride (1.77mL, 0.011mole) , Yield: 94% (0.85g) UV (methanol) λmax 357nm; IR(nujol) ν 3120, 3026, 2910, 1521, 1431, 1327, 655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (s, 2H), 4.38 (s, 2H), 7.12 (s, 1H) , 7.45 (m, 10H);ppm ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.85, 38.97, 124.94, 126.10, 131.09, 132.68, 134.67, 160.34 ppm.

1-chloro-3-[(1-[(3-chlorophenyl)methyl]sulfanyl-2-nitroeth-1-enyl)sulfanyl]methylbenzene (10)
3-Chlorobenzyl chloride (1.77mL, 0.01mole), Yield: 94% (0.77g) UV (methanol) λmax 357nm; IR(nujol) ν 3122, 3020, 2960, 1529, 1433, 1323, 675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (s, 2H), 4.23 (s, 2H), 7.13 (s, 1H) , 7.35 (m, 10H);ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.94, 39.02, 126.33, 129.38, 130.37, 134.63, 136.18, 159.76ppm.

ANTIMICROBIAL ACTIVITY STUDY
The anti bacterial activity for the compounds **(3-10)** was determined by Disc-Diffusion method. The antibacterial activity studies in nutrient agar medium for the following organisms *Escherichia coli*, *Proteus sp*, *Serratia marcescens*, *Pseudomonas aureginosa*, *Citrobactor sp*, *Klebsiella pneumonia*, *Bacillus subtills*, *Micrococcus*, *Staphylococcus aureus and Staphylococcus viridians* were carried out.

PREPARATION OF NUTRIENT AGAR MEDIUM
Exactly 1g of peptone 0.5g of Beef extract and 0.5 g of sodium chloride were weighed and transferred into conical flask and dissolved in 100ml of distilled water after the pH range was checked for 7.0 – 7.2 finally added 1.5 g of agar into the conical flask. It was closely packed with cotton plug and placed in an autoclave for 15 minutes for sterilization. 100mL of nutrient agar medium was poured into the petri plates and allowed for solidification without any disturbance. The test organism was lawned on the surface of the agar medium using a cotton swap . The

concentration of 100µg of all the derivatives between **(3)** and **(10)** was loaded on the empty discs using micropipette. The loaded sterile disc was placed in the culture lawned medium and incubated in the inverted position for 16-18 hours at 35°C. 100µg of Chloramphenicol loaded discs were used as standard drugs. The results were reported in the **Table – I**.

Table I: Anti bacterial activity of Nitroketene dithioacetal derivatives (3-10)

Name of the Culture	Zone of Inhibition in mm for derivatives **(3-10)**								Standard
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Chloramphenicol
Escherichia coli	14	10	16	13	16	16	15	14	21
Proteus sp	12	8	9	10	10	14	13	16	19
Serratia marcescens	14	12	12	14	13	13	17	14	20
Pseudomonas aeruginosa	9	11	14	11	15	19	24	18	27
Citrobactor sp	12	9	10	14	13	14	18	16	22
Klebsiella pneumoniae	13	8	12	14	11	14	15	17	19
Bacillus subtilis	14	12	14	12	15	15	13	15	17
Micrococcus	10	10	13	14	13	12	18	16	23
Staphylococcus aureus	11	10	9	13	15	15	16	17	21
Staphylococcus viridans	14	14	14	11	12	12	15	16	18

** Excluding the diameter of the disc (5mm)*

RESULTS AND DISCUSSION

Alkyl and aryl substituted derivatives of nitroketene dithioacetals **(3-10)** were synthesized by a two step process by condensing nitromethane **(1)** with Carbon disulfide **(2)** in presence of methanolic KOH followed by the treatment of appropriate alkyl and chloro substituted benzyl bromides in presence of 60% aqueous acetone for 12hrs. **(Scheme – I)**. The formation of the products (**3-10)** were monitored by TLC and further purified by Column Chromatography. The structure of the compounds 4-10 were identified by ^{1}H NMR, ^{13}C NMR, IR and UV spectral evidences.

The UV spectral λ max value in the range of 356 nm showed the presence of extensive conjugation between the lone pair of electron in sulfur and the nitro group for the compounds(**4-10).** The IR band at 1525 $^{cm-1}$ and 1452 $^{cm-1}$ showed the presence of nitro group (-NO_2) in the products. The presence of olefinic proton band (=C-H) was observed at 3060^{cm-1}. Aliphatic proton bands in the case of (**4-7)** were observed at 2994, 2928, and 2923 $^{cm-1}$. The presence of aromatic proton band in the case of compounds 8-10 was observed at 3132, 3120 and 3122 $^{cm-1}$.

The olefinic protons in ^{1}HNMR were appeared at 7.12 ppm range for the compounds(**8-10)** and for the compounds (**4-7)** in the range of 7.06 ppm. The *[Z]* S- substituted α- protons were resonated at 2.53, 2.04 and 3.33 ppm for the compounds **(4-6)**. The *[E]* S-substituted α- protons were resonated slightly downfield at 2.54, 3.01 and 3.63 ppm for the compounds 4-6. The *[Z]* S-substituted benzylic methylene protons were resonated at 4.15, 4.16 and 4.16 ppm for the compounds 8-10. The *[E]* S- substituted benzylic methylene protons were resonated slightly downfield at 4.22, 4.38 and 4.23 ppm for the compounds 8-10. Similarly in ^{13}CNMR the olefinic carbon atoms were appeared in the range of 125ppm for the compounds (**4-10)**. The quaternary carbon in the olefin was observed in the range of 160ppm for the compounds **(4-10)**. The newly formed 1,3-dithiole product 7 showed the olefinic proton peak at 6.96 ppm and the dithiole ring proton peak at 7.71ppm as expected. The olefinic carbon ^{13}CNMR showed the olefinic carbon at 12.5 ppm and the 1,3-dithiole ring proton substituted carbon at 123.6ppm.

Among the nine synthesised compounds **6, 7, 9** and **10** were newly reported and the structures were characterized for the first time remaining compounds were reported earlier in the literature. The antibacterial activity studies for the compounds **(3-10)** were reported for the first time in this report following Disc-Diffusion method in nutrient agar medium. All the compounds were screened against *Escherichia coli, Proteus sp, Serratia marcescens, Pseudomonas aureginosa, Citrobactor sp, Klebsiella pneumonia, Bacillus subtills, Micrococcus, Staphylococcus aureus and Staphylococcus viridians.* Compound (**9)** and **(10)** showed good anti bacterial activity and all other compounds between 3 and 8 showed moderately good activities.

CONCLUSION

The present work was focused to synthesis S,S-bis substituted derivatives of nitroketene dithioacetals with alkyl **(4-7)** and benzyl **(8)** and Chloro substituted benzyl **(9-10).** Among the synthesised derivatives 4,5and 8 were reported

earlier in the literature and the remaining derivatives **6,7,9** and **10** were reported for the first time. The antibacterial activities for the series of derivatives (3-10) were screened for the first time with ten different types of bacteria. Chloramphenicol was used as reference standard. From the result it is found and reported that alkyl group substitution on the sulfur atoms of nitroketene dithioacetal motif in respect of derivatives 4-7 showed moderate antibacterial activity than the dipotassium salt of nitroketene dithioacetal motif **(3)** and benzyl group substitution **(8-10)** on the sulfur atom of the nitroketene dithioacetal motif showed good antibacterial activity.

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