Tetrahedron Vol. 49, No 10, pp. 2101-2108, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Unique Zeolite-catalyzed Synthesis of Nitroketene S,N-Acetals#

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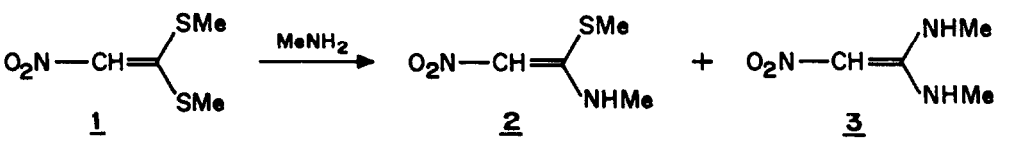
(*Received in UK 7 December* 1992)

Abstract: Dimethyl carbonimidodithioates (**4a-g, 7a-c**) derived from various primary amines and amino acid esters [glycine, (L)-alanine and (L)-phenylalanine] have been condensed with nitromethane in the presence of the rare-earth exchanged zeolite RE(70%)Na Y to give the S,N-acetals (**5a-g, 8a-c**). Mercuric chloride catalyzed hydrolysis of these (**8a-c**) has led to the nitroacetyl derivatives (**9a-c**). The glycine derivative (**7a**) gives a dimeric product (**11**) when heated alone with the zeolite.

Nitroketene S,N-acetals are useful intermediates for the construction of several nitroheterocycles[1,2]. One of the simplest members of this class of compounds, 1-methylamino-1-methylthio-2-nitroethylene (**2**) is a crucial intermediate in the synthesis of the anti-ulcer drug, Ranitidine[3]. There have been only two general methods described so far for the synthesis of such compounds[2]. In the first method, nitromethane is added to an isothiocyanate in presence of base (sodium hydride) and the adduct methylated. This route is only applicable if the required isothiocyanates are readily available; it cannot be the method of choice if the isothiocyanates themselves have to be synthesised first. The second method depends on the reaction of a nitroketene S,S-acetal (**1**) with one equivalent of a primary or secondary amine. Thus the Ranitidine intermediate (**2**) has been prepared by treatment of



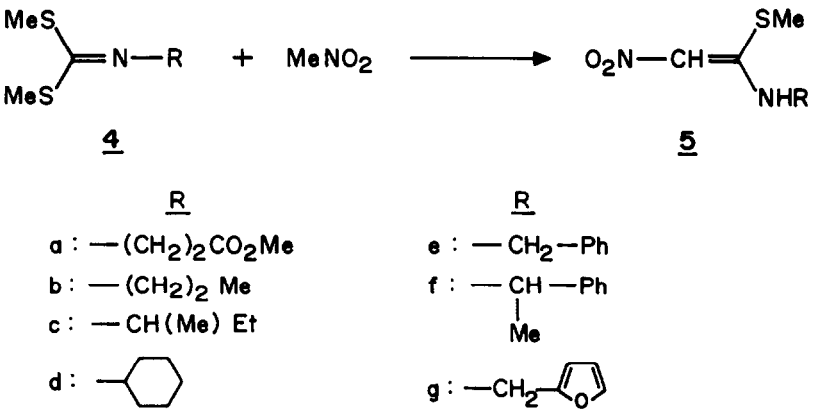
1 **2** **3**

1,1-bismethylthio-2-nitroethylene (**1**) with methylamine. However, it has been our experience, and that of others[4] that in this method, the further reaction of **2** with another molecule of methylamine to form the 1,1-bismethylamino-2-nitroethylene (**3**) cannot be avoided. Furthermore, the 1,1-bismethylthio-2-nitroethylene (**1**) used in this route is prepared by a known method[5] involving base-catalysed condensation of nitromethane; the drawback in this method is that it involves the use of nitromethane in an alkaline medium, a situation known to be hazardous[6].

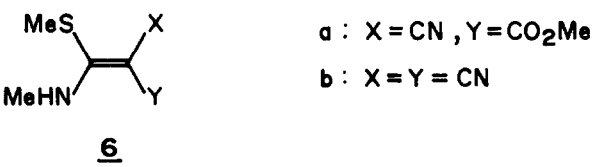
NCL Communication No. 5575

We now report another approach to the synthesis of nitroketene S,N-acetals which avoids both the drawbacks mentioned above. This synthetic route depends on the condensation of nitromethane with various carbonimidodithioic acid dimethyl esters (Scheme 1). An earlier literature report[7] had described the condensation

Scheme 1



of active methylene compounds such as cyanoacetic ester or malononitrile with N-methyl carbonimidodithioic acid dimethyl ester (**4**; **R** = **Me**) (no catalyst; reaction temperature 80 to 120 °C) to form **6a** and **6b** respectively.

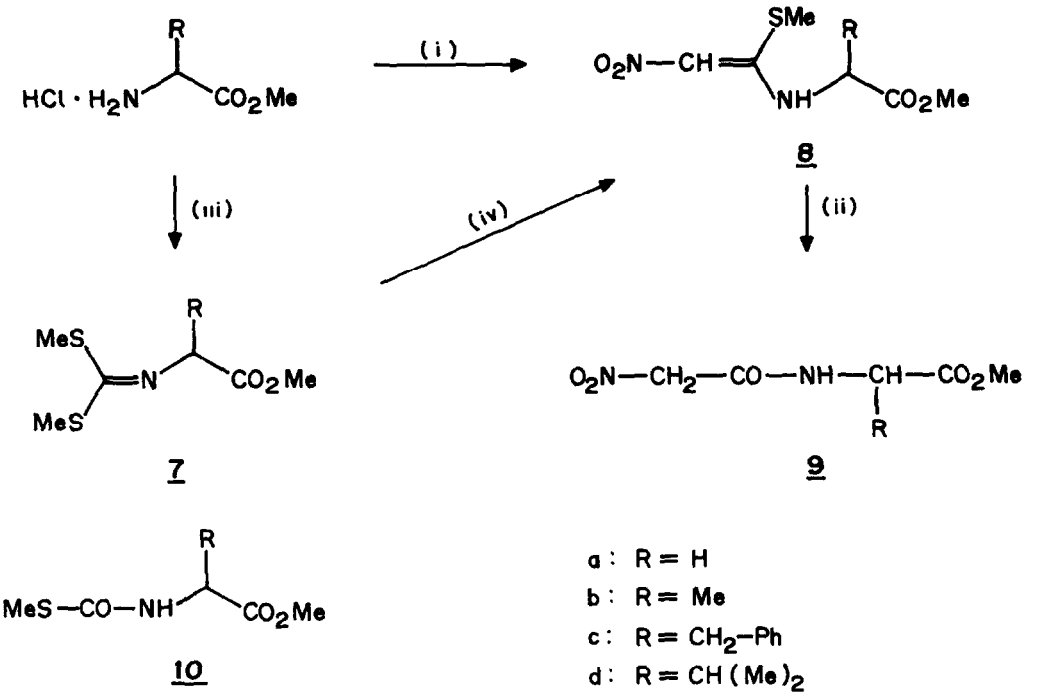


Initially, we attempted to exploit this reaction for the synthesis of the Ranitidine intermediate (**2**). However, nitromethane refused to undergo condensation with dimethyl N-methyl carbonimidodithioate (**4**, **R** = **Me**) under the same condition; nor could the reaction be induced to occur by conventional Lewis acid or base catalysis. Successful condensation between the two reactants to produce **2** (=**5**, **R** = **Me**) in 50% yield was finally achieved by us by employing a rare-earth exchanged zeolite as the catalyst[8]. The catalyst was prepared by exchanging commercial Na Y zeolite with a mixture of rare-earth chlorides[9].

The scope of the zeolite-catalysed condensation has now been fully explored. The carbonimidodithioates (**4a-g**) have been successfully condensed with nitromethane to give the nitroketene S,N-acetals (**5a-g**) in 52 to 86% yields.

The condensation could also be extended to the carbonimidodithioates (**7a-c**) derived from α-amino acid esters. This gave us a useful alternate route to N-nitroacetyl derivatives (**9**) of the α-amino acid esters (***Scheme 2***). Such nitroacetyl derivatives could be valuable intermediates in the synthesis of peptides incorporating unusual α-mono substituted or α,α-disubstituted glycine residues[10].

Scheme 2



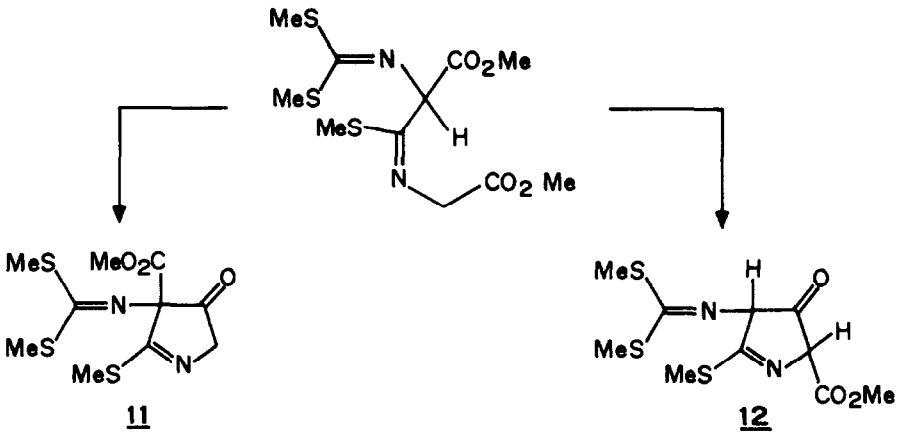
Reagents and conditions: (i) O_2N-CH=C $(SMe)_2$/MeCN, PTSA (catalytic), 50 °C, 12-15 h; (ii) $HgCl_2$/ MeCN : H_2O (3:1), 50-60 °C, 4-6 h; (iii) a) CS_2, Et_3N/CH_2Cl_2, 30 min then MeI, Reflux, 2-3 h; b) Et_3N, MeI, Reflux, 2-4 h; (iv) $MeNO_2$, RE(70%)Na Y, Reflux, 24 h.

Methyl esters of glycine, (L)-alanine, (L)-phenylalanine and (L)-valine were condensed with carbon disulfide by the usual procedure[11] with appropriate modifications, and then methylated to give the corresponding carbonimidodithioates (**7a-d**). The glycine, alanine and phenylalanine derivatives (**7a-c**) were then reacted with nitromethane (excess nitromethane, reflux) in presence of the rare-earth exchanged Na Y catalyst (RE(70%)Na Y) to give the nitroketene S,N-acetals (**8a-c**) in 25-65% yield. The reaction failed in the case of the valine derivative (**7d**), perhaps due to steric reasons, the isopropyl group probably hindering access to the zeolite cavity. These compounds **8** were then subjected to Hg^{2+} catalysed hydrolysis; this led to the desired nitroacetamides **9** (**a-c**). Earlier a few similar nitroketene S,N-acetals had been made by us by the reaction of corresponding α-amino acid esters (L-proline, L-valine and L-phenylalanine) with 1,1-bismethylthio-2-nitroethylene (**Scheme 2**)[10,12]. The overall yield of **8c** (40.5% in two steps) by the present route is definitely better than that obtained in the earlier method (~25% in two steps). However, while the present route has not been successful with valine, the earlier one gave a 30% yield of **8d** (ethyl ester instead of methyl ester).

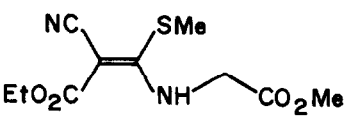
A minor by-product in each one of the above condensation reactions between nitromethane and (**7**) was the corresponding S-methyl thiolcarbamate (**10a-d**) arising by hydrolysis of the carbonimidodithioate[13]. Apart from these, an unexpected crystalline by-product was obtained in 52% yield in the reaction of the glycine derivative (**7a**) with nitromethane in presence of the zeolite. The same product was obtained in 72% yield when nitromethane was omitted and the sole reactant (**7a**) refluxed in toluene solution in presence of the zeolite. Combustion data and the mass spectrum (molecular ion at m/z 306) led to the formula $C_{10}H_{14}N_2O_3S_3$ for the product, thus indicating that

it was obtained from two molecules of the starting material. It is known that the methylene group of compounds such as (**7a**) can be deprotonated and could act as a nucleophilic site[14]; the carbon atom of the imine group is, of course, an electrophile. Initial bond-formation between these two carbon atoms, followed by appropriate cyclisation can lead to either of two structures (**11**) or (**12**) (*Scheme 3*). The ^{1}H NMR spectrum of the product consisted of only the following five singlets: 4.34 (2H), 3.76 (3H), 2.76 (3H), 2.64 (3H) and 2.58 (3H). In the ^{13}C NMR spectrum, employing the DEPT technique, the CH_2 group resonated at 41.26 ppm. The above NMR data clearly proved structure (**11**) for the product. This unique dimerization of the glycine derivative (**7a**) has not been observed before with conventional basic catalysts; zeolite, again, seems to be a specific catalyst for this process.

Scheme 3



It is perhaps pertinent to speculate at this stage on the role of the zeolite in bringing about this condensation. We have cited two examples in this article which are specifically brought about by zeolite catalysis, but not by Lewis acids or bases. We suspect that the availability of multicatalytic sites in the zeolite cavity is responsible for the success with this. It is not too difficult to visualize the two reactant molecules being held close to each other in the cavity, a proton being abstracted from the active methylene (or methyl) of one and being delivered to the imine nitrogen of the other, thereby facilitating C-C bond formation.



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The glycine derivative (**7a**) did not react with methyl nitroacetate; only the self-condensed product (**11**) was formed in this reaction. However, ethyl cyanoacetate reacted to give S,N-acetal (**13**) in 80% yield.

Experimental Section

General: Zeolite RE(~70%)Na Y freshly activated at 400 °C for 4 h was used in all experiments. All the chemicals used in this study were commercial grade and used after distillation. Melting points were determined with microscope hot stage apparatus and are uncorrected. All purifications were carried out by column chromatography using 100-200 mesh silica gel activated at 100 °C for 2 h with EtOAc-hexane mixture as the eluent. ^1H & ^{13}C NMR spectra were recorded with $CDCl_3$ as solvent and TMS as internal standard.

Rare Earth exchange of zeolite Na Y: Na Y zeolite was equilibrated with an aqueous solution of Didymium chloride[9] to obtain about 70% rare-earth exchange[15].

General procedure for the synthesis of dimethyl carbonimidodithioates of various primary amines and amino acid methyl esters (4a-g, 7a-d): To a solution of primary amine or amino acid ester hydrochloride (10 mmol) and carbon disulfide (10 mmol) in methylene dichloride (50 ml), triethylamine (11 mmol, additional 10 mmol of triethylamine was used in case of amino acid ester hydrochloride) was added slowly at 20 °C. The reaction mixture was stirred for 30 min at room temperature. Methyl iodide (12 mmol) was then added dropwise and the resulting mixture was refluxed for 2-3 h. The reaction mixture was then cooled to room temperature; triethylamine (12 mmol), methyl iodide (12 mmol) were successively added dropwise and it was again refluxed for 2-4 h. After complete conversion of dithiocarbamate to carbonimidodithioate, the reaction mixture was cooled, washed with water (2 X 30 ml) and concentrated under vacuum. The residue was taken in ether (50 ml) and again washed with water (3 X 20 ml) and brine, dried (anhyd Na_2SO_4) and concentrated to give the product (**4a-g, 7a-d,**) in 70-90% yield.

N-[Bis (methylthio) methylene]β-alanine methyl ester (4a): Yield 87%; Colourless liquid, b.p. 101 °C/4.5 mm; ^1H **NMR** (90 MHz): δ 3.70 (s, 3H, OCH_3), 3.65 (t, J = 6.9 Hz, 2H, NCH_2), 2.65 (t, *J* = 6.9 Hz, 2H, $COCH_2$), 2.50 (s, 3H, SCH_3) 2.35 (s, 3H, SCH_3); **IR** ($CHCl_3$): 1745, 1590 cm^{-1}; **MS:** *m/z* 207 (M^+, 05%), 160 (90), 87 (100); Anal. Calcd for $C_7H_{13}NO_2S_2$: C, 40.57; H, 6.28; N, 6.76. Found: C, 40.31; H, 6.44; N, 6.78.

N-n-Propyl carbonimidodithioic acid dimethyl ester (4b): Yield 72%; Yellow coloured liquid, b.p. 47 °C/0.17 mm; ^1H **NMR** (80 MHz): δ 3.40 (t, *J* = 7.2 Hz, 2H, NCH_2), 2.55 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 1.65 (m, 2H, CH_2), 1.00 (t, *J* = 7.2 Hz, 3H, CH_3); **IR** (Neat): 1590 cm^{-1}; **MS:** *m/z* 163 (M^+, 20%), 116 (100), 74; Anal. Calcd for $C_6H_{13}NS_2$: C, 44.17; H, 7.97; N, 8.58. Found: C, 43.98; H, 8.02; N, 8.27.

N-sec-Butyl carbonimidodithioic acid dimethyl ester (4c): Yield 78%; Yellow coloured liquid, b.p. 61 °C/0.21 mm; ^1H **NMR**(80 MHz): δ 3.70 (m, 1H), 2.50 (s, 3H, SCH_3), 2.30 (s, 3H, SCH_3), 1.45 (m, 2H, CH_2), 1.10 (d, *J* = 6.4 Hz, 3H, CH_3), 0.80 (t, *J* = 7.2 Hz, 3H, CH_3); **IR** (Neat): 1600 cm^{-1}; **MS:** *m/z* 177 (M^+, 05%), 130 (70), 74 (100); Anal Calcd for $C_7H_{15}NS_2$: C, 47.45; H, 8.47; N, 7.90. Found: C, 47.57; H, 8.51; N, 8.02.

N-Cyclohexyl carbonimidodithioic acid dimethyl ester (4d): Yield 84%; Colourless liquid, b.p. 93 °C/4.5 mm; ^1H **NMR** (80 MHz): δ 3.60 (m, 1H, NCH), 2.55 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 1.20-1.80 (br, m, 10H). **IR** (Neat): 1590 cm^{-1}; **MS:** *m/z* 203 (M^+, 10%), 156 (100), 83, 74; Anal. Calcd for $C_9H_{17}NS_2$: C, 53.20; H, 8.37; N, 6.89. Found: C, 52.91; H, 8.26; N, 7.10.

N-Benzyl carbonimidodithioic acid dimethyl ester (4e): Yield 82%; Yellow coloured liquid, bp. 124 °C/4.5 mm; ^1H **NMR** (80 MHz): δ 7.30 (m, 5H, aromatic), 4.60 (s, 2H, NCH_2), 2.55 (s, 3H, SCH_3), 2.40 (s, 3H, SCH_3); **IR** (Neat): 1590 cm^{-1}; **MS:** *m/z* 211 (M^+, 05%), 164 (60), 91 (100); Anal. Calcd for $C_{10}H_{13}NS_2$: C, 56.87; H, 6.16; N, 6.63. Found: C, 56.53; H, 6.71; N, 6.72.

(S)-N-α-Methylbenzyl carbonimidodithioic acid dimethyl ester (4f): Yield 86%; Yellow coloured liquid, b.p. 105 °C/4.7 mm; ^1H **NMR** (200 MHz): δ 7.40 (m, 5H, aromatic), 4.95 (q, *J* = 6.3 Hz, 1H), 2.60 (s, 3H, SCH_3) 2.50 (s, 3H, SCH_3), 1.50 (d, *J* = 6.3 Hz, 3H, CH_3); **IR** (Neat): 1585 cm^{-1}; **MS:** *m/z* 225 (M^+, 00%), 178 (20), 105 (100); Anal. Calcd for $C_{11}H_{15}NS_2$: C, 58.66; H, 6.66; N, 6.22. Found: C, 59.09; H, 7.06; N, 6.57.

(±)-N-α-Methylbenzyl carbonimidodithioic acid dimethyl ester (4f): Yield 88%; Yellow coloured liquid, b.p. 121 °C/4.4 mm; Anal. Calcd for $C_{11}H_{15}NS_2$: C, 58.66; H, 6.66; N, 6.22. Found: C, 58.84; H, 6.91; N, 6.55.

N-Furylmethyl carbonimidodithioic acid dimethyl ester (4g): Yield 75%; Light yellow coloured liquid, b.p. 100 °C/4.65 mm; ^{1}H NMR (200 MHz): δ 7.30 (m, 1H), 6.30 (m, 2H,), 4.55 (s, 2H, CH_2), 2.50 (s, 3H, SCH_3), 2.30 (s, 3H, SCH_3); IR (Neat): 1595 cm^{-1}; MS: *m/z* 201 (M^+, 05%), 153 (50), 81 (100); Anal. Calcd for $C_8H_{11}NOS_2$: C, 47.76; H, 5.47; N, 6.96. Found: C, 47.92; H, 5.73; N, 6.84.

N-[Bis (methylthio) methylene] glycine methyl ester (7a): Yield 70%; Yellow coloured liquid, b.p. 110 °C/1.5 mm; ^{1}H NMR (90 MHz): δ 4.20 (s, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 2.55 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3); IR (Liq.film): 1755, 1585 cm^{-1}; MS: *m/z* 193 (M^+, 20%), 146 (100); Anal. Calcd for $C_6H_{11}NO_2S_2$: C, 37.30; H, 5.69; N, 7.25. Found: C, 37.58; H, 5.83; N, 7.44.

N-[Bis (methylthio) methylene](L)-alanine methyl ester (7b): Yield 82%; Colourless liquid, b.p. 94 °C/4.5 mm; ^{1}H NMR (80 MHz): δ 4.55 (q, J = 7.2 Hz, 1H), 3.75 (s, 3H, OCH_3), 2.40 (s, 3H, SCH_3), 2.20 (s, 3H, SCH_3), 1.45 (d, J = 7.2 Hz, 3H, CH_3); IR (Neat): 1750, 1580 cm^{-1}; MS: *m/z* 207 (M^+, 10%), 160 (100), 132; Anal. Calcd for $C_7H_{13}NO_2S_2$: C, 40.57; H, 6.28; N, 6.76. Found: C, 39.95; H, 6.90; N, 6.76.

N-[Bis (methylthio) methylene](L)-phenylalanine methyl ester (7c): Yield 90%; Colourless crystalline solid, m.p. 49-51 °C; ^{1}H NMR (80 MHz): δ 7.30 (s, 5H, aromatic), 4.70 (m, 1H), 3.70 (s, 3H, OCH_3), 3.15 (m, 2H), 2.40 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3); IR (Nujol): 1735, 1575 cm^{-1}; MS: *m/z* 283 (M^+, 05%), 236 (100); Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.12; H, 6.00; N, 4.94. Found: C, 55.27; H, 6.24; N, 4.94.

N-[Bis (methylthio) methylene](L)-valine methyl ester (7d): Yield 84%; Colourless liquid, b.p. 90 °C/5.2 mm; ^{1}H NMR (80 MHz): δ 4.20 (d, J = 6.4 Hz, 1H), 3.70 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3) 2.40 (s, 3H, SCH_3), 2.30 (m, 1H), 1.00 (d, J = 6.8 Hz, 6H); IR (Neat): 1750, 1590 cm^{-1}; MS: *m/z* 235 (M^+, 00%), 188 (100); Anal. Calcd for $C_9H_{17}NO_2S_2$: C, 45.95; H, 7.23; N, 5.95. Found: C, 45.79; H, 7.84; N, 6.08.

General procedure for the preparation of nitroethylene compounds 5a-g and 8a-c from carbonimidodithioic acid dimethyl esters 4a-g and 7a-c: Freshly activated zeolite RE(~70%)Na Y (0.5g) was added to the mixture of **4a-g** and **7a-c** (10 mmol) and nitromethane (50 mmol) at room temperature and the suspension was refluxed with stirring for 24 h. The reaction mixture was then cooled to room temperature, the catalyst was filtered and washed with CH_2Cl_2 (2 X 30 ml). The filtrate was concentrated at reduced pressure. The residue was taken in n-hexane and stirred for a few min to solidify the product. Final purification was carried out by column chromatography to give the pure product (**5a-g** and **8a-c**) in 25-82% yield.

Methyl N-[1-(Methylthio)-2-nitroethenyl]β-alaninate (5a): Yeild 62%; an oil; ^{1}H NMR (80 MHz): δ 10.70 (br, 1H, NH), 6.60 (S, 1H), 3.75, (s, 3H, OCH_3), 3.70 (m, 2H, NCH_2), 2.70 (t, J = 6.4 Hz, 2H, $COCH_2$), 2.45 (s, 3H, SCH_3); IR ($CHCl_3$): 3300-3500, 1740, 1570 cm^{-1}; MS: *m/z* 220 (M^+, 15%), 173, 87 (100), 59; Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.18; H, 5.45; N, 12.72. Found: C, 38.13; H, 5.55; N, 12.81.

1-Methylthio-1-n-propylamino-2-nitroethylene (5b): Yield 76%; Colourless crystalline solid, m.p. 63-64 °C (EtOH); ^{1}H NMR (80 MHz): δ 10.60 (br, 1H, NH), 6.60 (s, 1H), 3.35 (q, 2H, NCH_2), 2.35 (s, 3H, SCH_3), 1.60 (m, 2H, CH_2), 1.00 (t, J = 6.72 Hz, 3H, CH_3); IR (nujol): 3400, 1570, 1470, 1380 cm^{-1}; MS: *m/z* 176 (M^+, 70%), 129, 87, 74 (100); Anal. Calcd for $C_6H_{12}N_2O_2S$: C, 40.90; H, 6.82; N, 15.90. Found: C, 41.43; H, 6.69; N, 16.22.

1-sec-Butylamino-1-methylthio-2-nitroethylene (5c): Yield 82%; Colourless crystalline solid, m.p. 116-118 °C (EtOH); ^{1}H NMR (90 MHz): δ 10.50 (br, 1H, NH), 6.55 (s, 1H), 3.70 (m, 1H), 2.45 (s, 3H, SCH_3), 1.60 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.00 (t, J = 7.2 Hz, 3H, CH_2CH_3); IR (Nujol): 3350-3450, 1560, 1470, 1330, 1230 cm^{-1}; MS: *m/z* 190 (M^+, 30%), 135, 74 (100), 57; Anal. Calcd for $C_7H_{14}N_2O_2S$: C, 44.21; H, 7.36; N, 14.73. Found: C, 44.32; H, 7.21; N, 14.57.

1-Cyclohexylamino-1-methylthio-2-nitroethylene (5d): Yield 75%; Colourless crystalline solid, m.p. 106 °C (EtOH); ^{1}H NMR (80 MHz): δ 10.50 (br, 1H, NH), 6.50 (s, 1H), 3.60 (m, 1H, NCH), 2.40 (s, 3H, SCH_3), 1.2-2.0 (br, 10H); IR (Nujol): 3300, 1570, 1480, 1230 cm^{-1}; MS: *m/z* 216 (M^+, 20%), 135 (100), 83, 55; Anal. Calcd for $C_9H_{16}N_2O_2S$: C, 50.00; H, 7.40; N, 12.96. Found: C, 50.21; H, 7.31; N, 13.11.

1-Benzylamino-1-methylthio-2-nitroethylene (5e): Yield 80%; Light yellow coloured solid, m.p. 104-105 °C (EtOH); ^{1}H NMR (200 MHz): δ 11.10 (br, 1H, NH), 7.40 (s, 5H, aromatic), 6.65 (s, 1H), 4.70 (d, J = 6.5 Hz, 2H, NCH_2), 2.40 (s, 3H, SCH_3); IR ($CHCl_3$): 3400, 1580, 1350 cm^{-1}; MS: *m/z* 224 (M^+, 10%), 178, 130, 91 (100); Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.35; N, 12.50. Found: C, 53.61; H, 5.42; N, 12.22.

(S)-1-α-Methylbenzylamino-1-methylthio-2-nitroethylene (5f): Yield 52%; Light yellow coloured solid, m.p. 44-45 °C (EtOH); ^{1}H NMR (200 MHz): δ 10.95 (br, 1H, NH), 7.35 (m, 5H, aromatic), 6.60 (s, 1H), 4.95 (m, 1H), 2.40 (s, 3H, SCH_3), 1.70 (d, J = 7.7 Hz, 3H, CH_3); IR ($CHCl_3$): 3440, 1580, 1360 cm^{-1}; MS: *m/z* 238 (M^+, 05%), 191, 105 (100); Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.46; H, 5.88; N, 11.76. Found: C, 55.38; H, 5.92; N, 11.91.

(±)-1-α-Methylbenzylamino-1-methylthio-2-nitroethylene (5f): Yield 50%; Light yellow coloured Crystalline solid, m.p. 119 °C; Anal. Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.46; H, 5.88; N, 11.76. Found: C, 55.32; H, 5.99; N, 11.97.

1-Furfurylamino-1-methylthio-2-nitroethylene (5g): Yield 78%; Gum; ^{1}H NMR (90 MHz): δ 10.55 (br, 1H, NH), 7.40 (m, 1H), 6.55 (s, 1H), 6.30 (m, 2H), 4.65 (d, J = 5.9 Hz, 2H, NCH_2), 2.47 (s, 3H, SCH_3); IR ($CHCl_3$): 3550-3450, 1570, 1360 cm^{-1}; MS: *m/z* 214 (M^+, 10%), 168, 81 (100); Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.67; N, 13.08. Found: C, 44.74; H, 4.79; N, 12.92.

Methyl N-[1-(Methylthio)-2-nitroethenyl]glycinate (8a): Yield 25%, (along with compound **11** was also isolated in 52% yield); Thick liquid; ^{1}H NMR (90 MHz): δ 10.55 (br, 1H, NH) 6.60 (s, 1H), 4.20 (d, J = 5.7 Hz, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 2.45 (s, 3H, SCH_3); IR ($CHCl_3$): 3300-3500, 1760, 1580 cm^{-1}; MS: *m/z* 206 (M^+, 30%), 159, 147, 131, 74 (100); Anal. Calcd for $C_6H_{10}N_2O_4S$: C, 34.95; H, 4.85; N, 13.59. Found: C, 35.12; H, 4.73; N, 13.67.

Methyl N-[1-(Methylthio)-2-nitroethenyl](L)-alaninate (8b): Yield 65%; Light yellow coloured crystalline solid, m.p 113-114 °C (EtOH); ^{1}H NMR (80 MHz): δ 10.70 (br, 1H, NH), 6.60 (s, 1H), 4.58 (m, 1H), 3.85 (s, 3H, OCH_3), 2.50 (s, SCH_3), 1.65 (d, J = 7.6 Hz, 3H, CH_3); IR ($CHCl_3$): 3280-3450, 1770, 1580, 1480 cm^{-1}; MS: *m/z* 220 (M^+, 25%), 174, 161, 141, 74 (100); Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.18; H, 5.45; N, 12.72. Found: C, 38.06; H, 5.57; N, 12.79.

Methyl N-[1-(Methylthio)-2-nitroethenyl](L)-phenylalaninate (8c): Yield 45%; Gum; ^{1}H NMR (200 MHz): δ 10.50 (br, 1H, NH), 7.10-7.30 (m, 5H, aromatic) 6.60 (s, 1H), 4.65 (m, 1H), 3.70 (s, 3H, OCH_3), 3.15 (m, 2H), 2.30 (s, 3H, SCH_3); IR ($CHCl_3$): 3500-3280, 1745, 1570 cm^{-1}; MS: *m/z* 296 (M^+, 15%), 237, 219, 176, 91 (100), 74; Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.70; H, 5.40; N, 9.45. Found: C, 52.82; H, 5.52; N, 9.59.

Dimethyl N-[3-(3-carbomethoxy-2-methylthio-4-keto-4,5-dihydro)-3(H)-pyrrolyl] carbonimidodithioate (11): A mixture of **7a** (1g), zeolite RE(70%)Na Y (0.5g) and toluene (10 ml) was refluxed for 24 h. The reaction mixture was then cooled to room temperature and the catalyst was filtered, washed with CH_2Cl_2 (3 x 20 ml). The filtrate was concentrated and the residue was taken in n-hexane. The solid product was isolated and purified by column chromatography to get a yellow coloured solid (**11**) in 72% yield; m.p. 119 °C (EtOH); ^{1}H NMR (300 MHz): δ 4.34 (s, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 2.76 (s, 3H, SCH_3), 2.64 (s, 3H, SCH_3), 2.58 (s, 3H, SCH_3); ^{13}C NMR (75.5 MHz): 167.40, 163.18, 155.55, 150.39, 134.47, 52.48, 41.25, 19.10, 18.24, 12.76; IR ($CHCl_3$): 1760, 1690, 1560 cm^{-1}; MS: *m/z* 306 (M^+, 100%), 245, 185, 118, 72, 61; Anal. Calcd for $C_{10}H_{14}N_2O_3S_3$: C, 39.21; H, 4.57; N, 9.15. Found: C, 39.19; H, 4.62; N 9.27.

Methyl N-[(1-methylthio-2-carbethoxy-2-cyano) ethenyl]glycinate (13): A mixture of **7a** (1 g, 5 mmol), ethyl cyanoacetate (5 mmol) and zeolite RE(70%)Na Y (0.5 g) was refluxed in toluene (15 ml) for 16 h. The reaction mixture was worked up according to the procedure described above for **11** to give light yellow coloured solid (**13**) in 80% yield; m.p. 127 °C (EtOH); ^{1}H NMR (90 MHz): δ 10.40 (br, 1H, NH), 4.30 (m, 4H, OCH_2 and NCH_2), 3.80 (s, 3H, OCH_3), 2.65 (s, 3H, SCH_3), 1.30 (t, J = 6.9 Hz, 3H, CH_3); IR ($CHCl_3$): 3000, 2210, 1750, 1660, 1580 cm^{-1}; MS: *m/z* 258 (M^+, 90%), 153 (100), 137 (95); Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.42; N, 10.85. Found: C, 46.78; H, 5.71; N, 10.86.

General procedure for the preparation of nitroacetamides (9a-c)[12]: To a solution of $HgCl_2$ (10 mmol) in CH_3CN:H_2O (3:1, 20 ml), a solution of **8a-c** (10 mmol) in the same solvent (20 ml) was added drop wise and the mixture was stirred for 4-6 h at 40-50 °C. The reaction mixture was cooled, and then filtered through celite pad and concentrated under vacuum. The residue was taken in $CHCl_3$ (40 ml) washed with water, dried (anhyd Na_2SO_4), concentrated and purified by column chromatography to get pure product (**9a-c**) in 85-90% yield.

Methyl N-(nitroacetyl)glycinate (9a): Yield 85%; Gum; ^{1}H NMR (80 MHz): δ 7.50 (br, 1H, NH), 5.25 (s, 2H), 4.15 (d, J = 5.7 Hz, 2H, NCH_2), 3.80 (s, 3H, OCH3); IR (Nujol): 3340, 1740, 1680, 1575 cm^{-1}; MS: *m/z* 176 (M^+, 10%), 117 (100); Anal. Calcd for $C_5H_8N_2O_5$: C, 34.09; H, 4.54; N, 15.90. Found: C, 34.12; H, 4.68; N, 16.12.

Methyl N-(nitroacetyl)(L)-alaninate (9b): Yield 88%; an oil; ^{1}H NMR (80 MHz): δ 7.35 (br, 1H, NH), 5.20 (s, 2H), 4.65 (m, 1H), 3.85 (s, 3H, OCH_3), 1.50 (d, J = 6.1 Hz, 3H, $CHCH_3$); IR (Nujol): 3300, 1750, 1680, 1570 cm^{-1}; MS: *m/z* 190 (M^+, 05%), 131 (100); Anal. Calcd for $C_6H_{10}N_2O_5$: C, 37.89; H, 5.26; N, 14.73. Found: C, 37.78; H, 5.38; N, 14.79.

Methyl N-(ntroacetyl)(L)-phenylalaninate (9c): Yield 90%; Crystalline solid, m.p. 79%; ^{1}H NMR (80 MHz): δ 10.50 (bs, 1H, NH), 7.30 (m, 5H, aromatic), 5.15 (s, 2H), 4.90 (m, 1H), 3.70 (s, 3H, OCH_3), 3.15 (m, 2H); IR (Nujol): 3320, 1740, 1670, 1570 cm^{-1}; MS: *m/z* 266 (M^+, 10%), 207, 176, 131, 91 (100); Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.26; N, 10.52. Found: C, 54.31; H, 5.28; N, 10.54.

Acknowledgment: We thank the CSIR for the award of a Research Fellowship to T.I.R.

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