Reaction of lactim ethers and lactim sulfides with electrophiles: attack at nitrogen followed by ring-opening under neutral conditions

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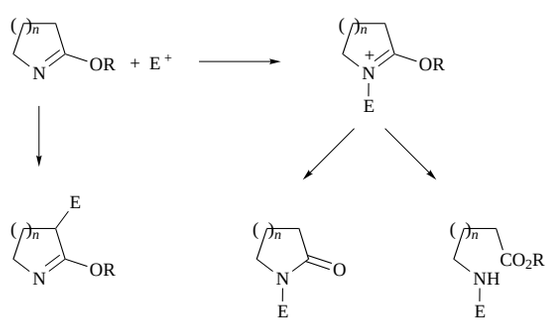
Electrophilic push-pull molecules react at the nitrogen of lactim ethers and lactim sulfides; subsequent hydrolysis gives ring-opened products in good yields.

Introduction

The reaction of lactim ethers (or sulfides) with electrophiles can take several routes, in most of which the nitrogen atom of the substrate acts as the nucleophile;[1] but this is not always the case. There are examples in the literature where C-3 is the site of electrophilic attack. This obviously results from the reaction of the lactim ether as its enamine tautomer. Thus, the five-membered γ-butyrolactim ether **1a** and its six-membered homologue **1b** react with aryl isocyanates at C-3 to form phenylcarbamoyl derivatives[2] (Scheme 1). The initial nucleophilic attack of one molecule of the lactim ether in its enamine form on another molecule of the lactim ether at the electrophilic carbon has been suggested to account for the products of the reaction of the lactim ether with diketene.[3] A further variation is provided by the corresponding lactim sulfide **2**. Thus, while the 5-membered lactim sulfide **2a** reacts with aryl isocyanates in the enamine form at C-3, the higher ring homologues **2b** and **2c** react at the nitrogen.[4] Subsequent deprotonation at C-3 leads to enaminoureas. Reaction at the nitrogen with electrophiles can have at least two other sequels. There are several examples in the literature in which the second step is the attack by the counterion on the alkyl group of the ether leading to *N*-substituted lactams *via* alkyl–oxygen cleavage (Scheme 1). This is the case with alkylation,[5] acylation[6] and sulfonylation.[7] Most interesting in the context of the present discussion are the occasional reports of the reaction of lactim ether with electrophiles followed by opening of the lactam ring (Scheme 1). Thus



Scheme 1

ω-isocyano carboxylic acid esters are reported to result from the reaction of lactim ethers with chloroform in aqueous alkali.[8] Similarly, the lactim ether **1c** reacts with thiophosgene to form an isothiocyanato carboxylic ester.[9] There is also a recent report that 1,4-naphthoquinone reacts with **1a** in methanol to form 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone.[10]

The present report deals with the reaction of lactim ethers and the corresponding sulfides with a series of electrophilic push-pull ethylenes in methanol solution. In all the examples studied, attack took place on the nitrogen atom; this was followed by opening of the ring, leading to the formation of carboxylic esters.

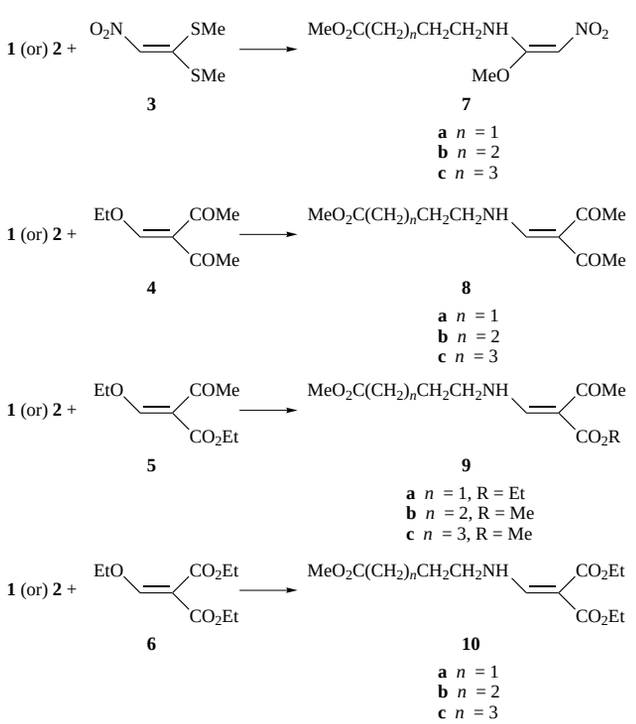
Results and discussion

Reaction of the five-, six- or seven-membered lactim ethers **1** or the corresponding sulfides **2** with a series of electrophilic push-

1 **2**

a *n* = 1
b *n* = 2
c *n* =3

pull ethylenes **3**–**6** in methanol solution led to the ring-opened products **7**–**10** in yields in the range 38–79% (Scheme 2). The



Scheme 2

lactim sulfides invariably gave higher yields of the product as compared to their oxygen counterparts. Thus, treatment of the γ-butyrolactim ether **1a** with 1,1-bismethylthio-2-nitroethylene **3** in refluxing methanol for 72 h gave methyl *N*-(1-methoxy-2-nitroethenyl)aminobutanoate **7a** in 43% yield. The inter-

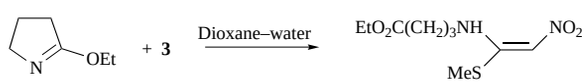
Table 1 Reaction of lactim ethers with electrophiles in refluxing methanol

Lactim ether	Electrophile	Duration of reaction (h)	Product	Yield (%)
1a	**3**	72	**7a**	43
1b	**3**	72	**7b**	50
1c	**3**	60	**7c**	56
1a	**4**	72	**8a**	48
1b	**4**	72	**8b**	53
1c	**4**	60	**8c**	68
1a	**5**	72	**9a**	38
1b	**5**	72	**9b**	55
1c	**5**	60	**9c**	57
1a	**6**	72	**10a**	40
1b	**6**	72	**10b**	60
1c	**6**	60	**10c**	55

Table 2 Reaction of lactim sulfides with electrophiles in refluxing methanol for 48 h

Lactim sulfides	Electrophile	Product	Yield (%)
2a	**3**	**7a**	64
2b	**3**	**7b**	65
2c	**3**	**7c**	75
2a	**4**	**8a**	71
2b	**4**	**8b**	70
2c	**4**	**8c**	79
2a	**5**	**9a**	66
2b	**5**	**9b**	64
2c	**5**	**9c**	70
2a	**6**	**10a**	68
2b	**6**	**10b**	60
2c	**6**	**10c**	67

mediacy of the corresponding methylthio compound was proved by carrying out the condensation of butyrolactim ethyl ether with **3** in dioxane–water instead of in methanol; under these conditions, the methylthio substituted nitroenamine **11** was obtained in 65% yield (Scheme 3). Reaction of the δ-



11

Scheme 3

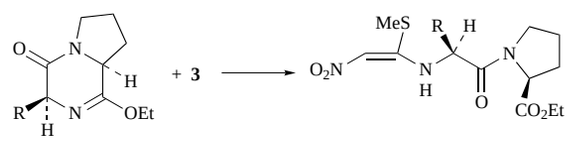
valerolactim ether **1b** and ε-caprolactim ether **1c** with 1,1-bismethylthio-2-nitroethylene **3** in refluxing methanol similarly gave **7b** and **7c** in 50 and 56% yields, respectively. As expected from the relative nucleophilicity of the nitrogen atom in lactim ethers and lactim sulfides, reaction of the sulfides **2a–c** with **3** under the same conditions led to higher yields of the products **7a–c**. In all these reactions, hydrolysis of the iminium ion obviously takes place by the water present in the solvent.[11]

It has been well established earlier that nitro enamines possessing an NH group exist almost exclusively in the intramolecularly hydrogen-bonded configuration, especially in non-polar solvents.[12] It is also known that the barrier to rotation around the formal double-bond in such systems is low enough to preclude isolation of the less energetically favoured geometrical isomer.[12] On this basis, the products **7a–c** have been assigned the *E* configuration (NH and NO_2 *cis* to each other).

The reaction took a similar course with other electrophilic push-pull ethylene systems as well. Thus ethoxymethyleneacetylactone **4** reacted with γ-butyrolactim ether **1a** in refluxing methanol to give **8a** (48%). The sulfide **2a** gave the same product (71%). δ-Valerolactim ether **1b** and ε-caprolactim ether **1c** condensed with **4** to give **8b** (53%) and **8c** (68%), respectively, while the corresponding sulfides **2b** and **2c** led to higher yields of the products. Tables 1 and 2 list the products and yields in these and other related condensations involving ring-opening.

The configuration around the double bond in the aminomethyleneacetoacetic ester derivatives **9** is uncertain, although even here, only one species was observed in the NMR spectra in $CDCl_3$ solution. Also in two of these products **9b** and **9c** trans-esterification had taken place under the reaction conditions, leading to methyl esters from ethyl ethoxymethyleneacetoacetate **5**.

One of our objectives in this area has been to utilise nitroketene *O,N*-acetals or *S,N*-acetals (such as **7** and **11**) for the synthesis of peptides incorporating non-natural α-alkylated amino acids. The route involves hydrolysis to the nitroacetamides and subsequent regiospecific alkylation of the reactive methylene group, followed by reduction of the NO_2 to NH_2.[13] Towards this end, we treated several cyclodipeptide mono iminoethers **12**[14] with 1,1-bismethylthio-2-nitroethylene **3** (Scheme 4), our hope being that the resulting nitroketene



12 **13**

Scheme 4

S,N-actals **13** could be hydrolysed to the corresponding nitroacetamides and then converted in two steps into modified tripeptides.

Unfortunately, the initial condensation was successful only with the cyclo (L-Pro-Gly) monoiminoether **12** (R = H), leading to **13** (R = H) (32%). The reaction failed with the analogous derivatives of alanine, valine, leucine or phenylalanine, in each case starting materials being recovered.

The ring-opening/*N*-alkylation reported above has potential in synthesis where the lactim ethers (or lactam) are more easily accessible than the corresponding ω-aminoalkyl carboxylic esters. Also, some of the latter may prefer to undergo intramolecular cyclisation to lactams under the reaction conditions.

Experimental

General

Melting points were determined with a microscope hot-stage apparatus, and are uncorrected. IR spectra were determined on a Perkin-Elmer-Infracord spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker-WH-90 (Spectrospin), Bruker-AC-200, Bruker-MSL-300 or Varian-FT-80A instrument in $CDCl_3$ solution with tetramethylsilane as internal standard. Coupling constants *J* are given in Hz. Mass spectra were determined on a Finnigan-MAT-1020B spectrometer. Microanalyses were performed at the Organic Chemistry Division, NCL.

Typical procedure

The lactim ethers were prepared according to the literature method;[15] thio lactams were obtained from their oxygen counterparts using Lawesson's reagent[16] and etherified by iodomethane in acetone in the presence of K_2CO_3.

The lactim ether or lactim sulfide (2 mmol) and the electrophile (2 mmol) were mixed in methanol (10 ml). The mixture was refluxed and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample was purified by column chromatography over silica gel using acetone–light petroleum.

Methyl 4-(1-methoxy-2-nitroethenylamino)butanoate 7a. A yellow oil (43%); ν_{max}/cm^{-1} (neat) 3360, 3260, 2960, 1740 and 1520; $\delta_H(CDCl_3)$ 1.9 (m, 2H, CH_2), 2.35 (t, 2H, $COCH_2$, *J* 8),

3.45 (q, 2H, NCH_2, *J* 7), 3.75 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 6.70 (s, 1H, =CH) and 9.85 (br s, 1H, NH); $\delta_C(CDCl_3)$ 24.22, 30.42, 39.43, 51.06, 56.57, 97.32, 164.26 and 172.44; *m/z* 218 (M^+), 187, 172, 140, 112 (100%) and 98 (Found: C, 43.99; H, 6.24; N, 12.60. $C_8H_{14}N_2O_5$ requires C, 44.03; H, 6.42; N, 12.84%).

Methyl 5-(1-methoxy-2-nitroethenylamino)pentanoate 7b. A yellow gum (50%); ν_{max}/cm^{-1} (neat) 3144, 2954, 1729, 1642, 1510 and 1380; $\delta_H(CDCl_3)$ 1.55–1.70 (m, 4H, 2 CH_2), 2.35 (t, 2H, $COCH_2$, *J* 5), 3.35 (q, 2H, NCH_2, *J* 7), 3.65 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.65 (s, 1H, =CH) and 9.85 (br s, 1H, NH); $\delta_C(CDCl_3)$ 21.80, 28.71, 33.11, 40.14, 51.22, 56.89, 97.57, 164.54 and 173.23; *m/z* 232 (M^+), 201, 186, 176, 154, 140, 112, 98 and 55 (100%) (Found: C, 46.52; H, 6.62; N, 12.08. $C_9H_{16}N_2O_5$ requires C, 46.55; H, 6.89; N, 12.06%).

Methyl 6-(1-methoxy-2-nitroethenylamino)hexanoate 7c. A brown gum (56%); ν_{max}/cm^{-1} (neat) 3250, 2960, 1745, 1630, 1520 and 1450; $\delta_H(CDCl_3)$ 1.40 (m, 2H, CH_2), 1.50–1.70 (m, 4H, 2 CH_2), 2.30 (t, 2H, $COCH_2$, *J* 8), 3.35 (q, 2H, NCH_2, *J* 7), 3.65 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.65 (s, 1H, =CH) and 9.85 (br s, 1H, NH); $\delta_C(CDCl_3)$ 23.48, 25.26, 28.24, 32.79, 39.63, 50.47, 56.26, 96.85, 163.85 and 172.83; *m/z* 246 (M^+), 229, 215, 200, 173, 168, 154, 131, 126, 112, 85 (100%) and 69 (Found: C, 48.73; H, 7.48; N, 11.23. $C_{10}H_{18}N_2O_5$ requires C, 48.78; H, 7.31; N, 11.38%).

Methyl 4-(2,2-diacetylethenylamino)butanoate 8a. A colourless oil (48%); ν_{max}/cm^{-1} (neat) 3200, 2920, 1730, 1640, 1600 and 1460; $\delta_H(CDCl_3)$ 1.95 (m, 2H, CH_2), 2.25 (s, 3H, $COCH_3$), 2.40 (t, 2H, $COCH_2$, *J* 8), 2.45 (s, 3H, $COCH_3$), 3.45 (q, 2H, NCH_2, *J* 7), 3.70 (s, 3H, OCH_3), 7.70 (d, 1H, =CH, *J* 14) and 11.00 (br s, 1H, NH); $\delta_C(CDCl_3)$ 24.91, 26.02, 29.59, 30.51, 48.15, 50.53, 110.22, 159.54, 171.82, 193.22 and 198.50; *m/z* 227 (M^+), 212, 196, 180, 154, 138, 126 (100%), 112 and 101 (Found: C, 58.15; H, 7.32; N, 6.05. $C_{11}H_{17}NO_4$ requires C, 58.14; H, 7.48; N, 6.16%).

Methyl 5-(2,2-diacetylethenylamino)pentanoate 8b. A colourless oil (53%); ν_{max}/cm^{-1} (neat) 3200, 2951, 2360, 1740, 1633 and 1390; $\delta_H(CDCl_3)$ 1.65 (m, 4H, 2 CH_2), 2.25 (s, 3H, $COCH_3$), 2.35 (t, 2H, $COCH_2$, *J* 6), 2.45 (s, 3H, $COCH_3$), 3.35 (q, 2H, $NHCH_2$, *J* 7), 3.65 (s, 3H, OCH_3), 7.70 (d, 1H, =CH, *J* 13) and 11.05 (br s, 1H, NH); $\delta_C(CDCl_3)$ 20.95, 26.30, 29.30, 30.80, 32.45, 48.89, 50.60, 110.30, 156.64, 172.48, 193.37 and 198.66; *m/z* 241 (M^+), 226, 210, 194, 152, 126 (100%), 112, 98 and 83 (Found: C, 59.95; H, 7.91; N, 5.72. $C_{12}H_{19}NO_4$ requires C, 59.75; H, 7.88; N, 5.80%).

Methyl 6-(2,2-diacetylethenylamino)hexanoate 8c. A colourless oil (68%); ν_{max}/cm^{-1} (neat) 3210, 2980, 1745, 1630, 1600, 1405 and 1320; $\delta_H(CDCl_3)$ 1.45 (m, 2H, CH_2), 1.65 (m, 4H, 2 CH_2), 2.25 (s, 3H, $COCH_3$), 2.35 (t, 2H, $COCH_2$, *J* 8), 2.50 (s, 3H, $COCH_3$), 3.35 (q, 2H, NCH_2, *J* 7), 3.65 (s, 3H, OCH_3), 7.75 (d, 1H, =CH, *J* 15) and 11.00 (br s, 1H, NH); $\delta_C(CDCl_3)$ 23.20, 24.75, 25.92, 29.19, 30.46, 32.45, 48.73, 50.17, 109.87, 159.38, 172.42, 193.08 and 198.31; *m/z* 255 (M^+), 240, 224, 198, 166, 154, 140, 126 (100%), 112, 96 and 69 (Found: C, 61.00; H, 8.59; N, 5.43. $C_{13}H_{21}NO_4$ requires C, 61.17; H, 8.23; N, 5.49%).

Methyl 4-(2-acetyl-2-ethoxycarbonylethenylamino)butanoate 9a. A colourless oil (38%); ν_{max}/cm^{-1} (neat) 3490, 3280, 2940, 1730, 1720, 1680, 1590 and 1540; $\delta_H(CDCl_3)$ 1.25–1.45 (m, 5H, CH_2, CH_3), 2.40 (t, 2H, $COCH_2$, *J* 8), 2.50 (s, 3H, $COCH_3$), 3.45 (q, 2H, NCH_2, *J* 7), 3.75 (s, 3H, OCH_3), 4.20 (q, 2H, OCH_2, *J* 8), 8.00 (d, 1H, =CH, *J* 14) and 11.00 (br s, 1H, NH); $\delta_C(CDCl_3)$ 25.29, 26.43, 30.04, 30.93, 48.64, 49.41, 51.09, 110.87, 159.88, 172.36, 194.10 and 199.48; *m/z* 257 (M^+), 243, 212, 196, 180, 164, 138 (100%), 124 and 110 (Found: C, 55.96; H, 7.15; N, 5.25. $C_{12}H_{19}NO_5$ requires C, 56.03; H, 7.39; N, 5.44%).

Methyl 5-(2-acetyl-2-methoxycarbonylethenylamino)pentanoate 9b. A colourless oil (55%); ν_{max}/cm^{-1} (neat) 3390, 2950, 1740, 1700, 1605 and 1430; $\delta_H(CDCl_3)$ 1.25–1.75 (m, 4H, 2 CH_2), 1.95 (s, 3H, $COCH_3$), 2.30 (t, 2H, $COCH_2$, *J* 6.5), 3.27 (q, 2H, NCH_2, *J* 5), 3.60 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 8.10 (d, 1H, =CH, *J* 12) and 11.10 (br s, 1H, NH); *m/z* 257 (M^+), 242, 211, 196, 182, 166, 137 (100%), 124 and 89 (Found: C, 56.18; H, 7.01; N, 5.62. $C_{12}H_{19}NO_5$ requires C, 56.03; H, 7.39; N, 5.44%).

Methyl 6-(2-acetyl-2-methoxycarbonylethenylamino)hexanoate 9c. A colourless oil (57%); ν_{max}/cm^{-1} (neat) 3300, 2960, 1740, 1650, 1615, 1450 and 1370; $\delta_H(CDCl_3)$ 1.55–1.85 (m, 6H, 3 CH_2), 2.20 (s, 3H, $COCH_3$), 2.30 (t, 2H, $COCH_2$, *J* 8), 3.35 (q, 2H, NCH_2, *J* 7), 3.65 (s, 3 H, OCH_3), 3.70 (s, 3H, OCH_3), 8.00 (d, 1H, =CH, *J* 14) and 12.45 (br s, 1H, NH); *m/z* 257, 243, 228, 212, 184, 170, 156, 142 and 96 (100%) (Found: C, 57.27; H, 7.46; N, 5.50. $C_{13}H_{21}NO_5$ requires C, 57.56; H, 7.74; N, 5.16%).

Methyl 4-(2,2-diethoxycarbonylethenylamino)butanoate 10a. A colourless oil (40%); ν_{max}/cm^{-1} (neat) 3290, 2950, 1740, 1650, 1620 and 1540; $\delta_H(CDCl_3)$ 1.15 (m, 6H, 2 CH_3), 1.90 (m, 2H, CH_2), 2.35 (t, 2H, $COCH_2$, *J* 8), 3.35 (q, 2H, NCH_2, *J* 7), 3.60 (s, 3H, OCH_3), 4.20 (m, 4H, 2 OCH_2), 7.50 (d, 1H, =CH, *J* 15) and 9.2 (br s, 1H, NH); $\delta_C(CDCl_3)$ 14.11, 25.74, 30.37, 50.44, 52.20, 54.70, 59.48, 60.31, 89.55, 159.81, 165.80, 169.01 and 172.68; *m/z* 287 (M^+), 261, 218, 203, 189, 175, 161, 145, 131, 115, 89 and 75 (100%) (Found: C, 54.13; H, 7.60. $C_{13}H_{21}NO_6$ requires C, 54.35; H, 7.31%).

Methyl 5-(2,2-diethoxycarbonylethenylamino)pentanoate 10b. A colourless oil (60%); ν_{max}/cm^{-1} (neat) 3287, 2952, 1736, 1656, 1430 and 1220; $\delta_H(CDCl_3)$ 1.30 (t, 6H, 2 CH_3, *J* 10), 1.70 (m, 4H, 2 CH_2), 2.35 (t, 2H, $COCH_2$, *J* 8), 3.35 (q, 2H, NCH_2, *J* 8), 3.70 (s, 3H, OCH_3), 4.20 (q, 4H, 2 CH_2, *J* 10), 7.95 (d, 1H, =CH, *J* 15) and 9.2 (br s, 1H, NH); $\delta_C(CDCl_3)$ 13.70, 13.74, 21.16, 29.67, 32.63, 48.62, 50.67, 58.63, 58.78, 88.84, 159.29, 165.28, 168.41 and 172.59; *m/z* 301 (M^+), 256, 224, 209, 154, 128, 96, 82 and 55 (100%) (Found: C, 56.08; H, 7.62; N, 4.44. $C_{14}H_{23}NO_6$ requires C, 55.81; H, 7.64; N, 4.65%).

Methyl 6-(2,2-diethoxycarbonylethenylamino)hexanoate 10c. A colourless oil (55%); ν_{max}/cm^{-1} (neat) 3300, 2980, 1730, 1630, 1570 and 1450; $\delta_H(CDCl_3)$ 1.14–1.40 (m, 8H, CH_2, 2 CH_3), 1.60 (m, 4H, 2 CH_2), 2.35 (t, 2H, $COCH_2$, *J* 8), 3.30 (q, 2H, $NHCH_2$, *J* 7), 3.60 (s, 3H, OCH_3), 4.25 (q, 4H, 2 OCH_2, *J* 8), 7.95 (d, 1H, =CH, *J* 16) and 9.15 (br s, 1H, NH); $\delta_C(CDCl_3)$ 14.06, 14.15, 24.12, 25.66, 30.14, 33.42, 49.21, 51.13, 59.21, 59.40, 89.28, 159.65, 165.88, 169.08 and 173.41; *m/z* 315 (M^+), 309, 296, 270, 238, 223, 195, 167, 154 (100%) and 128 (Found: C, 56.85; H, 7.72; N, 4.21. $C_{15}H_{25}NO_6$ requires C, 57.14; H, 7.93; N, 4.44%).

Ethyl 4-(1-methylthio-2-nitroethenylamino)butanoate 11. A brown gum (65%); ν_{max}/cm^{-1} (neat) 3280, 2980, 2920, 1730, 1580, 1460 and 1420; $\delta_H(CDCl_3)$ 1.25 (t, 3H, CH_3, *J* 8), 2.00 (m, 2H, CH_2), 2.40 (t, 2H, $COCH_2$, *J* 8), 2.45 (s, 3H, SCH_3), 3.45 (q, 2H, NCH_2, *J* 7), 4.10 (q, 2H, OCH_2, *J* 8), 6.55 (s, 1H, =CH) and 10.50 (br s, 1H, NH); $\delta_C(CDCl_3)$ 13.72, 13.87, 24.00, 30.64, 43.34, 60.21, 105.86, 164.67 and 171.97; *m/z* 248 (M^+), 231, 215, 202, 157, 147, 119, 115, 101, 87 (100%) and 73 (Found: C, 43.72; H, 6.79; N, 11.17. $C_9H_{16}N_2O_4S$ requires C, 43.54; H, 6.45; N, 11.29%).

Ethyl 1-(1-methylthio-2-nitroethenylamino)acetylpyrrolidine-2-carboxylate 13 (R=H). A yellow solid (32%); mp 85–87 °C (EtOH); ν_{max}/cm^{-1} (Nujol) 3210, 2950, 1745, 1630, 1505, 1410 and 1380; $\delta_H(CDCl_3)$ 1.30 (t, 3H, CH_3, *J* 10), 1.85–2.30 (m, 4H, 2 CH_2), 2.45 (s, 3H, SMe), 3.60 (q, 2H, OCH_2, *J* 9), 4.10–4.35 (m, 5H, $NHCH_2$, NCH_2, NCHCO), 6.60 (s, 1H, =CH) and 10.70 (br s, 1H, NH); *m/z* 317 (M^+), 299, 271, 223, 199, 125, 98, 83 and 70 (100%) (Found: C, 45.38; H, 5.59. $C_{12}H_{19}N_3O_5S$ requires C, 45.42; H, 5.99%).

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