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Acylation of alkylidenepyrrolidines with heterocumulenes—a reinvestigation

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Abstract—The reactions of alkylidenepyrrolidine esters with isocyanates generally favour C-acylation, except in the case of benzyl isocyanate. Reactions with alkyl isocyanates are slow, and require forcing conditions. Reactions with isothiocyanates give exclusively the C-acylated products.
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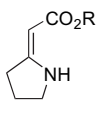
1. Introduction

Alkylidenepyrrolidines **1** are versatile heterocyclic ambident nucleophiles, which have been extensively used in organic synthesis.[1] During the course of our studies towards the synthesis of the batzelladine alkaloids,[2] we had occasion to undertake a three-component coupling reaction of an alkylidenepyrrolidine with an aldehyde and a silyl isothiocyanate.[3] Since the stereoselectivity in this reaction was modest, we sought an understanding of the mechanism in order to optimise this. For this study, we required a range of compounds of general structure **2** in order to study the stereoselectivity of their reactions with aldehydes. The N-acylation of alkylidenepyrrolidines has been reported with a range of alkyl and aryl isocyanates.[4] However, when we attempted to repeat some of the reactions in this report, we observed somewhat different results. In order to verify the trends observed during this work, a number of additional heterocumulenes were also investigated. We now report our results herein.



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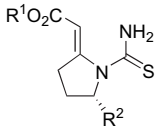

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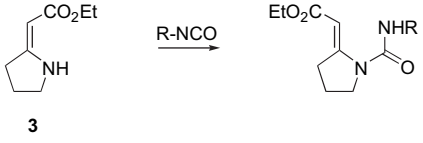
2. Results and discussion

The publication by Tronche[4] states that in general, all isocyanates used gave an approximately 70:30 mixture of products favouring N-acylation. With alkyl isocyanates, reactions were carried out in pyridine at room temperature for 2 h, while reactions with aryl isocyanates were undertaken in benzene at reflux (12 h). The examples reported are shown in Scheme 1.

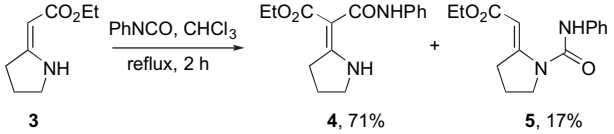


3

R = Me, *n*-Bu, *n*-C_6H_{13}, *c*-C_6H_{11}, Bn, Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-$CH_3C_6H_4$

Scheme 1.

In our hands, reaction of phenyl isocyanate with (*Z*)-alkylidenepyrrolidine **3** in chloroform under reflux gave a 3.4:1 crude mixture of C- and N-acylated products **4** and **5**. The isolated yields approximately reflect this regioselectivity (Scheme 2). At room temperature in the same solvent, a 2.1:1 mixture of the same compounds was obtained. When benzene (reflux) was used as solvent, a 5.2:1 mixture was obtained, while THF (also at reflux) gave the highest selectivity at 7:1. In all cases, the C-acylated product **4** predominated.



3 **4**, 71% **5**, 17%

Scheme 2.

All compounds in our study have been fully characterised (^{1}H NMR, ^{13}C NMR+DEPT, IR, MS, HRMS). The ^{1}H NMR

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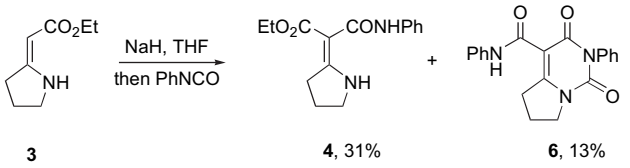
and melting point data which we have obtained for compound **5** are entirely in line with those reported by Tronche.[4] In an attempt to favour N-acylation, compound **3** was deprotonated with sodium hydride prior to reaction with phenyl isocyanate. However, this gave only a mixture of compound **4** and the novel heterocycle **6** (Scheme 3). Clearly the formation of compound **6** requires N-acylation, but this could occur after the C-acylation. In no case have we been able to obtain a mixture favouring the N-acylated product **5**.

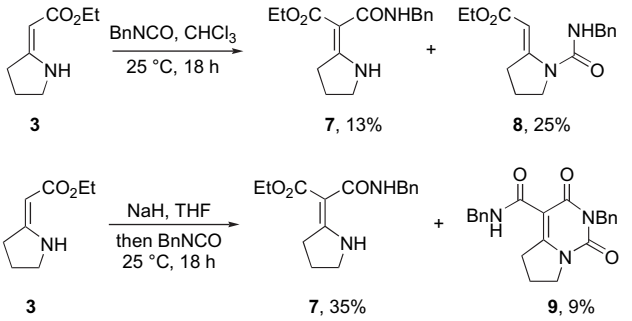


3 **4**, 31% **6**, 13%

Scheme 3.

In contrast, reaction of alkylidenepyrrolidine **3** with benzyl isocyanate proceeds to give a 2:1 mixture of N-acylated compound **8** and C-acylated compound **7**, exactly as reported.[4] We chose to carry out this reaction in chloroform rather than pyridine, and obtained poor conversion (Scheme 4). Upon heating, the overall yields were dramatically improved at the expense of regioselectivity (1:1). Deprotonation of the alkylidenepyrrolidine with sodium hydride gave good selectivity for C-acylation (5.3:1). In this case, the bicyclic compound **9** was also formed (9% yield), while the low conversion meant that compound **8** was not actually isolated.

At this point we felt that we were beginning to establish a trend, and that alkyl isocyanates would give predominantly N-acyl products while aryl isocyanates would give predominantly C-acyl products. In order to verify this, reactions were carried out with cyclohexyl and butyl isocyanates. In both

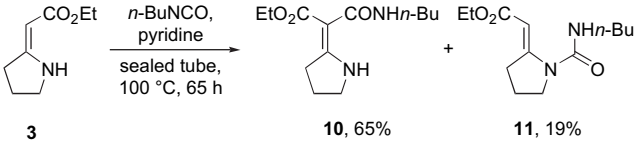


3 **7**, 13% **8**, 25%

3 **7**, 35% **9**, 9%

Scheme 4.

cases, no reaction was observed in either chloroform or pyridine at room temperature. With butyl isocyanate, upon heating for 65 h at 100 °C, C-acylation was again found to predominate (Scheme 5).



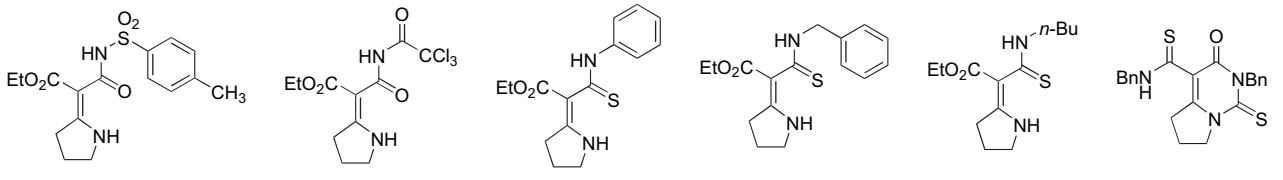
3 **10**, 65% **11**, 19%

Scheme 5.

Following on from these results, a number of other isocyanates and some isothiocyanates were investigated in this reaction. The results are summarised in Table 1. Of these other compounds, only 4-methylphenyl isocyanate was found to produce any of the N-acylated product, this being the minor compound produced. As we have previously discussed,[2] we believe that the data reported by Tronche for the N-acylated

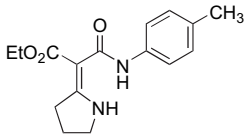
Table 1. Reactions of alkylidenepyrrolidine **3** with a range of heterocumulenes

Entry	Heterocumulene	Conditions	Ratio C:N acylation	Products (% isolated yield)
1	PhNCO	$CHCl_3$, 25 °C, 18 h	2.1:1	**4** (53%); **5** (20%)
2	PhNCO	$CHCl_3$, reflux, 2 h	3.4:1	**4** (71%); **5** (17%)
3	PhNCO	Benzene, reflux, 2 h	5.2:1	Not purified
4	PhNCO	THF, reflux, 2 h	7:1	Not purified
5	PhNCO	NaH, THF, 18 h	1:0	**4** (31%); **6** (13%)
6	BnNCO	$CHCl_3$, 25 °C, 18 h	1:2	**7** (13%); **8** (25%)
7	BnNCO	$CHCl_3$, reflux, 20 h	1:1	**7** (39%); **8** (50%)
8	BnNCO	NaH, THF, 18 h	5.3:1	**7** (35%); **9** (9%)
9	*n*-BuNCO	Pyridine, 100 °C, 65 h	2.3:1	**10** (65%); **11** (19%)
10	4-MeC_6H_4NCO	$CHCl_3$, reflux, 2 h	2.3:1	**12** (56%); **13** (23%)
11	TsNCO	$CHCl_3$, 25 °C, 2 h	1:0	**14** (94%)
12	$Cl_3CCONCO$	$CHCl_3$, 25 °C, 18 h	1:0	**15** (51%)
13	PhNCS	$CHCl_3$, reflux, 18 h	1:0	**16** (58%)
14	BnNCS	$CHCl_3$, reflux, 18 h	1:0	**17** (66%)
15	*n*-BuNCS	Pyridine, 100 °C, 46 h	1:0	**18** (89%)
16	BnNCS	NaH, THF, 18 h	1:0	**17** (38%); **19** (25%)



14 **15** **16** **17** **18** **19**

product **13** are actually more consistent with the C-acylated product **12**, so that our results are actually in agreement. In particular, the melting point reported for compound **13** is close to that which we have measured for compound **12**. In all other cases, the C-acylated product was formed exclusively, and in each case as a single double-bond isomer according to the spectroscopic data. The double-bond geometry is presumed to be that shown as a result of more favourable hydrogen bonding.[5]



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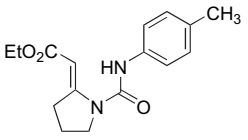
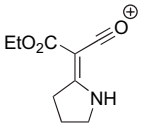


13

With the benefit of hindsight, it is straightforward to distinguish the C- and N-acyl compounds by mass spectrometry (electrospray or APCI). The former all give a strong peak at *m*/*z* 182 corresponding to fragment **20**, while the latter all give a peak at *m*/*z* 156, which presumably corresponds to **21**.



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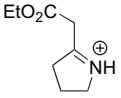
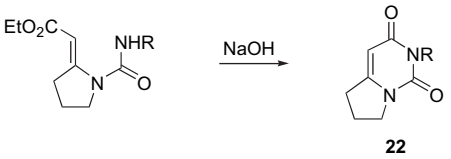


21

Tronche's group subsequently reported the formation of pyrrolo[1,2-*c*]pyrimidines **22** as shown in Scheme 6.[6] All of these compounds presented plausible NMR and analytical data, and it is difficult to see how any of these compounds could have been formed from the C-acyl isomers. We therefore have no doubt that the N-acyl compounds were indeed formed, although particularly in the case of R=*n*-Bu and *c*-C_6H_{13}, we are unable to reproduce their formation. The alkylidenepyrrolidine literature shows numerous examples of subtle reactivity,[7] so it seems possible that impurities present in either Tronche's or our own starting materials could affect the regioselectivity.



22

R = Me, *n*-C_4H_9, *n*-C_6H_{13}, *c*-C_6H_{11}, Bn, Ph

Scheme 6.

The other factor which could affect the regiochemical outcome is the double-bond geometry in the alkylidenepyrrolidine. Earlier reports[8] from the group of Tronche state that the (*Z*)-alkylidenepyrrolidine **3** gives exclusively the C-acylation product with methyl and phenyl isocyanates, while an unspecified mixture of (*E*) and (*Z*) isomers leads to the 70:30 mixture favouring N-acylation. In their 1988 paper,[4] Tronche and co-workers do state that a mixture of double-bond isomers was used. However, they prepared alkylidenepyrrolidine **3** by an Eschenmoser sulfide contraction, which is known to strongly favour the (*Z*)-alkylidenepyrrolidine,[1] and indeed the authors state in their experimental section that the (*Z*) isomer **3** was isolated in 46% yield, while the (*E*) isomer was unstable and was not isolated under these conditions.[4] Assuming that the (*Z*) isomer **3** and (*E*) isomer give C- and N-acylation products respectively, it is difficult to see how a mixture favouring the (*Z*) isomer could possibly give a 70:30 mixture favouring N-acylation. We are only aware of a single unequivocal example of the synthesis of the (*E*) isomer of a simple NH alkylidenepyrrolidine.[9] While many authors do draw the (*E*) isomer, it seems likely that this is for convenience, and generally no comment is made about the double-bond geometry. In the cases where the (*E*) isomer has been drawn and spectroscopic data are presented, all of these compounds appear to be the (*Z*) isomer.

Based on these observations, we can offer no conclusive explanation for the discrepancies between our own results and those of Tronche. Nevertheless, our results have proven to be reproducible and consistent over a range of heterocumulenes, and with batches of alkylidenepyrrolidine **3** prepared on a number of different occasions. We therefore feel that the results reported herein represent the norm for the acylation of alkylidenepyrroldines with heterocumulenes.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of dry nitrogen. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in parts per million downfield from TMS. Coupling constants (*J*) are reported in hertz. Multiplicity in ^{13}C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 μm. Compound **3** was prepared according to a literature method.[10]

3.1.1. *N*-Phenyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (4) and (1-phenylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (5). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (106 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added phenyl isocyanate (89 μL, 0.8 mmol), and the mixture stirred at 25 °C for 18 h. The solvent was then removed in vacuo. The resulting orange oil was purified by column chromatography (eluting with ethyl acetate/hexane 4.5:7) to give compound **4** (R_f=0.8) (99 mg, 53%) and compound **5** (R_f=0.37) (38 mg, 20%).

Data for compound **4**: yellow solid, mp 76–78 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3236, 1650, 1614; δ_H (400 MHz; $CDCl_3$) 11.44 (1H, br s, CH_2NH), 11.29 (1H, br s, PhNH), 7.50 (2H, d, *J* 7.6, aromatic CH), 7.21 (2H, apparent t, *J* 7.9, aromatic CH), 6.95 (1H, t, *J* 7.4, aromatic CH), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.52 (2H, t, *J* 7.7, CH_2NH), 3.11 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.91 (2H, m, CH_2CH_2NH), 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.9 (CH_2CNH), 169.9 ($C{=}O$), 168.9 ($C{=}O$), 139.2 (aromatic C), 128.7 (aromatic CH), 123.0 (aromatic CH), 120.6 (aromatic CH), 87.0 ($COCCO_2Et$), 59.9 ($CO_2CH_2CH_3$), 47.7 (CH_2NH), 36.5 ($CH_2C{=}C$), 21.3 (CH_2CH_2NH), 14.6 ($CO_2CH_2CH_3$); *m*/*z* (ES^+) 297.2 (MNa^+, 7%), 275.3 (MH^+, 2), 183.1 (28), 182.1 (100), 154.0 (99), 138.0 (98); HRMS (ES^+) calcd for $C_{15}H_{19}N_2O_3$ (MH^+) 275.1396, found 275.1373.

Data for compound **5**: colourless solid, mp 127–129 °C (lit.[4] mp 128 °C); ν_{max} (CH_2Cl_2)/cm^{-1} 3377, 1689, 1660, 1594; δ_H (400 MHz; $CDCl_3$) 7.31 (2H, d, *J* 7.7, aromatic CH), 7.22 (2H, apparent t, *J* 7.9, aromatic CH), 7.01 (1H, t, *J* 7.4, aromatic CH), 6.95 (1H, br s, NHPh), 6.34 (1H, apparent d, *J* 1.6, CH=C), 4.03 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.64 (2H, t, *J* 7.1, CH_2NCO), 3.12 (2H, apparent dt, *J* 1.6, 7.8, $CH_2C{=}C$), 1.87 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO), 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$). δ_C (100 MHz; $CDCl_3$) 168.9 (ester $C{=}O$), 158.2 (alkene C), 152.1 (urea $C{=}O$), 137.5 (aromatic C), 129.0 (aromatic CH), 124.3 (aromatic CH), 120.7 (aromatic CH), 95.6 (alkene CH), 59.4 (CO_2CH_2), 49.4 (CH_2NCO), 31.9 ($CH_2C{=}C$), 21.1 (CH_2CH_2NCO), 14.5 (CH_3CH_2OCO); *m*/*z* (ES^+) 275 (MH^+, 55%), 156 (100); HRMS (ES^+) calcd for $C_{15}H_{19}N_2O_3$ (MH^+) 275.1396, found 275.1397.

3.1.2. 1,3-Dioxo-2-phenyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid phenylamide (6). To a stirred suspension of sodium hydride (60% dispersion in oil, 35 mg, 1.5 mmol) in dry THF (15 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (207 mg, 1.3 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Phenyl isocyanate (159 mg, 1.3 mmol) was added, and the mixture stirred for 18 h at rt. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer extracted, and the aqueous layer washed with DCM (3×30 mL). The combined organic washings were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent removed in vacuo. The residue was recrystallised from ethanol to give the *title compound* (60 mg, 13%) as a pale yellow solid, mp 253–255 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3239, 1705, 1682, 1591, 1437; δ_H (400 MHz; $CDCl_3$) 11.12 (1H, br s, PhNHCO), 7.60–7.35 (5H, m, aromatic CH), 7.30–7.15 (4H, m, aromatic CH), 7.00 (1H, t, *J* 7.3, aromatic CH), 4.00 (2H, t, *J* 7.5, CH_2NCO), 3.77 (2H, t, *J* 7.9, $CH_2C{=}C$), 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2NCO); δ_C (100 MHz; $CDCl_3$) 164.9 ($C{=}O$), 163.5 ($C{=}O$), 160.6 ($C{=}O$), 147.8 (CH_2CNCO), 137.2 (aromatic C), 133.4 (aromatic C), 128.7 (aromatic CH), 128.3 (aromatic CH), 127.9 (aromatic CH), 127.1 (aromatic CH), 123.0 (aromatic CH), 119.3 (aromatic CH), 100.3 (NHCO–*C*–CO), 48.2 (CH_2NCO), 33.4 ($CH_2C{=}C$), 19.4 (CH_2CH_2NCO); *m*/*z* (ES^+) 370.3 (MNa^+, 92%), 348.3 (MH^+, 100), 273.2 (44), 255.2 (95); HRMS (ES^+) calcd for $C_{20}H_{18}N_3O_3$ (MH^+) 348.1348, found 348.1343. Purification of the filtrate by flash column chromatography gave compound **4** (113 mg, 31%) (data as above).

3.1.3. *N*-Benzyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (7) and (1-benzylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (8). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (103 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added benzyl isocyanate (80 μL, 0.7 mmol), and the mixture stirred at 25 °C for 18 h. The solvent was then removed in vacuo and the resulting orange oil purified by column chromatography (eluting with ethyl acetate/hexane 3:7) giving, in order of elution, compound **7** (R_f=0.41) (25 mg, 13%) and compound **8** (R_f=0.18) (48 mg, 25%).

Data for compound **7**: yellow solid, mp 95–98 °C; ν_{max} (Nujol)/cm^{-1} 3408, 1639, 1594; δ_H (400 MHz; $CDCl_3$) 11.40 (1H, s, CH_2NH), 9.51 (1H, m, $PhCH_2NH$), 7.27–7.18 (5H, m, aromatic CH), 4.43 (2H, d, *J* 5.7, $PhCH_2NH$), 4.09 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.50 (2H, t, *J* 7.4, CH_2NH), 3.09 (2H, t, *J* 7.9, $CH_2C{=}C$), 1.92 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH), 1.22 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.4 (CH_2CNH), 170.5 ($C{=}O$), 169.7 ($C{=}O$), 139.6 (aromatic C), 128.5 (aromatic CH), 127.3 (aromatic CH), 126.8 (aromatic CH), 86.6 ($COCCO_2Et$), 59.5 ($CO_2CH_2CH_3$), 47.5 ($PhCH_2NH$), 43.0 (CH_2NH), 36.2 ($CH_2C{=}C$), 21.4 (CH_2CH_2NH), 14.6 ($CO_2CH_2CH_3$); *m*/*z* (ES^+) 311 ($MNa+H_2O^+$, 26%), 289 (MH^+, 10), 243 (5), 182 (100); HRMS (ES^+) calcd for $C_{16}H_{22}N_2O_3$ (MH^+) 289.1552, found 289.1548.

Data for compound **8**: colourless solid, mp 88–92 °C, lit.[4] mp 86 °C; ν_{max} (Nujol)/cm^{-1} 3357, 1669, 1604; δ_H (400 MHz; $CDCl_3$) 7.28–7.14 (5H, m, aromatic CH), 6.41 (1H, apparent t, *J* 1.7, CH=C), 5.32 (1H, br s, $NHCH_2Ph$), 4.38 (2H, d, *J* 5.6, $NHCH_2Ph$), 4.02 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.54 (2H, t, *J* 7.1, CH_2NCO), 3.11 (2H, apparent dt, *J* 1.7, 7.8, $CH_2C{=}CH$), 1.87 (2H, apparent quintet, *J* 7.5, CH_2CH_2NCO), 1.16 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 169.1 (ester $C{=}O$), 158.3 (CH_2CNCO), 154.5 (urea $C{=}O$), 158.5 (aromatic C), 128.7 (aromatic CH), 127.7 (aromatic CH), 127.5 (aromatic CH), 95.0 ($CH{=}C$), 59.2 ($CO_2CH_2CH_3$), 49.1 ($NHCH_2Ph$), 44.5 (CH_2NCO), 31.8 ($CH_2C{=}C$), 21.1 (CH_2CH_2NCO), 14.5 ($CO_2CH_2CH_3$); *m*/*z* (ES^+) 329 (M+Na+H_2O, 65%), 261 (38), 156 (100), 128 (97); HRMS (ES^+) calcd for $C_{16}H_{22}N_2O_3$ (MH^+) 289.1552, found 289.1548.

3.1.4. 1,3-Dioxo-2-benzyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzylamide (9). To a stirred suspension of sodium hydride (60% dispersion in oil, 45 mg, 1.1 mmol) in dry THF (15 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (159 mg, 1.0 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Benzyl isocyanate (0.13 mL, 1.0 mmol) was added, and the mixture stirred for 18 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent

removed in vacuo. The resulting orange solid was purified by column chromatography (eluting with 3:7 ethyl acetate/hexane) giving, in order of elution, compound **9** (R_f=0.57) (36 mg, 9%) and compound **7** (R_f=0.41) (103 mg, 35%) (data as above).

Data for compound ***9***: yellow solid, mp 117–120 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3248, 1705, 1646, 1623, 1545, 1442; δ_H (400 MHz; $CDCl_3$) 11.10 (1H, br s, CH_2NHCO), 7.31 (4H, apparent t, *J* 7.6, aromatic CH), 7.26–7.12 (6H, m, aromatic CH), 5.04 (4H, apparent s, 2×PhCH_2N), 3.64 (2H, t, *J* 7.6, CH_2NCO), 3.39 (2H, t, *J* 8.0, CH_2C=C), 2.06 (2H, apparent quintet, *J* 7.8, CH_2CH_2NCO); δ_C (100 MHz; $CDCl_3$) 177.2 (Cl_3CC=O), 165.2 (C=O), 162.4 (C=O), 151.6 (CH_2CNCO), 137.6 (aromatic C), 137.6 (aromatic C), 128.5 (aromatic CH), 128.4 (aromatic CH), 128.2 (aromatic CH), 127.4 (aromatic CH), 127.3 (aromatic CH), 88.5 (NHCO–C–CO), 48.2 (CH_2NCO), 44.19, 44.16 (2×PhCH_2N), 35.3 (CH_2C=C), 20.8 (CH_2CH_2NCO); *m/z* (ES$^+$) 376 (MH$^+$, 100%), 310 (32), 238 (23), 123 (66); HRMS (ES$^+$) calcd for $C_{22}H_{22}N_3O_3$ (MH$^+$) 376.1661, found 376.1657.

3.1.5. *N*-Butyl-2-pyrrolidin-(2*E*)-ylidene-malonamic acid ethyl ester (10) and (1-*n*-butylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (11). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (147 mg, 0.9 mmol) in pyridine (0.5 mL) was added butyl isocyanate (128 μL, 1.1 mmol). The solution was stirred at 100 °C in a sealed tube for 65 h, after which time the solvent was removed under reduced pressure. The resulting dark brown oil was purified by column chromatography (eluting with ethyl acetate/hexane 4:7), to give compound **10** (R_f=0.33) (156 mg, 65%) and compound **11** (R_f=0.11) (45 mg, 19%) both as pale yellow oils.

Data for compound ***10***: pale yellow oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3314, 1654, 1598; δ_H (400 MHz; $CDCl_3$) 11.45 (1H, br s, CH_2NH), 9.10 (1H, br s, CH_2NHCO), 4.10 (2H, q, *J* 7.1, CO_2CH_2), 3.51 (2H, t, *J* 7.4, CH_2NH), 3.21 (2H, apparent q, *J* 6.5, CH_2NHCO), 3.08 (2H, t, *J* 7.9, CH_2C=C), 1.93 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH), 1.46 (2H, apparent quintet, *J* 7.3, $CH_3CH_2CH_2$), 1.31 (2H, apparent sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.85 (3H, t, *J* 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 174.1 (CH_2CNH), 170.3 (C=O), 169.6 (C=O), 86.5 (COCCO$_2$Et), 59.3 (CO_2CH_2), 47.3 (CH_2NH), 38.6 (CH_2NHCO), 36.0 (CH_2C=C), 31.8 ($CH_3CH_2CH_2$), 21.3 (CH_2CH_2NH), 20.3 ($CH_3CH_2CH_2$), 14.4 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); *m/z* (APCI) 255 (MH$^+$, 24%), 182 (100); HRMS (ES$^+$) calcd for $C_{13}H_{23}N_2O_3$ (MH$^+$) 255.1709, found 255.1704.

Data for compound ***11***: pale yellow oil; ν_{max} (CH_2Cl_2)/cm^{-1} 3348, 1646, 1565; δ_H (400 MHz; $CDCl_3$) 6.28 (1H, br s, alkene CH), 4.97 (1H, br s, NHCON), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.56 (2H, t, *J* 7.1, CH_2NCO), 3.21 (2H, apparent q, *J* 6.6, CH_2NHCO), 3.13 (2H, t, *J* 7.7, CH_2C=C), 1.89 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO), 1.47 (2H, apparent quintet, *J* 7.4, $CH_3CH_2CH_2$), 1.29 (2H, apparent sextet, *J* 7.4, $CH_3CH_2CH_2$), 1.18 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.87 (3H, t, *J* 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 169.0 (ester C=O), 158.4 (CH_2CNCO), 154.4 (urea C=O), 94.3 (CHCCO$_2$Et), 59.2 (CO_2CH_2), 49.2 (CH_2NCO), 40.4 (CH_2NHCO), 32.0 (CH_2C=C), 31.9 ($CH_3CH_2CH_2$), 21.1 (CH_2CH_2NH), 20.9 ($CH_3CH_2CH_2$), 14.5 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); *m/z* (APCI) 273 (M+H$_3$O$^+$, 42%), 255 (MH$^+$, 19%), 227 (16), 156 (100); HRMS (ES$^+$) calcd for $C_{13}H_{23}N_2O_3$ (MH$^+$) 255.1709, found 255.1704.

3.1.6. 2-Pyrrolidin-(2*E*)-ylidene-*N*-*p*-tolyl-malonamic acid ethyl ester (12) and (1-*p*-tolylcarbamoyl-pyrrolidin-(2*E*)-ylidene)-acetic acid ethyl ester (13). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (161 mg, 1 mmol) in $CHCl_3$ (6 mL) was added *p*-tolyl isocyanate (130 μL, 1 mmol), and the solution stirred under reflux for 2 h. The solvent was removed in vacuo to produce a yellow oil, which solidified on standing. The yellow solid was purified by column chromatography (eluting with EtOAc/hexane 4.5:7) giving, in order of elution, compound **12** (R_f=0.76) (168 mg, 56%) and compound **13** (R_f=0.29) (69 mg, 23%).

Data for compound ***12***: pale yellow solid, mp 150–153 °C; ν_{max} (solution)/cm^{-1} 3216, 1649, 1619; δ_H (400 MHz; $CDCl_3$) 11.40 (1H, br s, CH_2NH), 11.25 (1H, br s, ArNH), 7.37 (2H, apparent d, *J* 7.4, aromatic CH), 7.01 (2H, apparent d, *J* 7.4, aromatic CH), 4.12 (2H, q, *J* 7.1, CO_2CH_2), 3.49 (2H, t, *J* 7.4, CH_2NH), 3.08 (2H, t, *J* 7.9, CH_2C=C), 2.20 (3H, s, CH_3Ar), 1.88 (2H, apparent quintet, *J* 7.7, CH_2CH_2NH), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.8 (CH_2CNH), 169.9 (C=O), 168.8 (C=O), 136.5 (aromatic C), 132.5 (aromatic C), 129.3 (aromatic CH), 120.4 (aromatic CH), 87.0 (COCCO$_2$Et), 59.8 (CO_2CH_2), 47.6 (CH_2NH), 36.5 (CH_2C=C), 21.3 (CH_2CH_2NH), 20.9 (CH_3Ar), 14.6 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 311 (MNa$^+$, 30%), 289 (MH$^+$, 30), 182 (100); HRMS (ES$^+$) calcd for $C_{16}H_{22}N_2O_3$ (MH$^+$) 289.1552, found 289.1537.

Data for compound ***13***: colourless solid, mp 132–135 °C, lit.[4] mp 155 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3448, 1694, 1609; δ_H (400 MHz; $CDCl_3$) 7.25 (2H, apparent d, *J* 8.3, aromatic CH), 7.04 (2H, apparent d, *J* 8.3, aromatic CH), 6.77 (1H, s, NHAr), 6.31 (1H, apparent t, *J* 1.6, CH=C), 4.04 (2H, q, *J* 7.1, CO_2CH_2), 3.66 (2H, t, *J* 7.1, CH_2NCO), 3.15 (2H, apparent dt, *J* 1.7, 7.8, CH_2C=C), 2.24 (3H, s, CH_3Ar), 1.90 (2H, apparent quintet, *J* 7.4, CH_2CH_2NCO), 1.17 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 168.8 (ester C=O), 158.1 (CH_2CNCO), 152.1 (urea C=O), 134.8 (aromatic C), 134.0 (aromatic CH), 129.5 (aromatic CH), 120.7 (aromatic CH), 95.4 (CH=C), 59.3 (CO_2CH_2), 49.4 (CH_2NCO), 32.0 (CH_2C=C), 21.1 (CH_2CH_2NCO), 20.8 (CH_3Ar), 14.5 ($CO_2CH_2CH_3$); *m/z* (ES$^+$) 311 (MNa$^+$, 22%), 289 (MH$^+$, 8), 156 (100), 110 (34); HRMS (ES$^+$) calcd for $C_{16}H_{20}N_2O_3Na$ (MNa$^+$) 311.1372, found 311.1356.

3.1.7. 3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(toluene-4-sulfonylamino)-propionic acid ethyl ester (14). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (102 mg, 0.7 mmol) in $CHCl_3$ (6 mL) was added *p*-tosyl isocyanate (100 μL, 0.7 mmol) and the mixture stirred at reflux for 2 h. The solvent was removed in vacuo to yield the *title compound* (220 mg, 94%) as a white crystalline solid, without need for further purification, mp 154–158 °C; ν_{max} (Nujol)/cm^{-1} 3447, 1644, 1594; δ_H (400 MHz; $CDCl_3$) 12.20

(1H, s, CH_2NH), 11.30 (1H, s, SO_2NHCO), 7.83 (2H, apparent d, J 8.3, aromatic CH), 7.18 (2H, apparent d, J 8.3, aromatic CH), 4.09 (2H, q, J 7.1, $CO_2CH_2CH_3$), 3.46 (2H, t, J 7.5, CH_2NH), 3.05 (2H, t, J 7.9, CH_2C=C), 2.29 (3H, s, CH_3Ar), 1.89 (2H, apparent quintet, J 7.7, CH_2CH$_2$NH), 1.20 (3H, t, J 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 175.9 (CH_2CNH), 169.5 (C=O), 167.7 (C=O), 143.9 (aromatic C), 137.4 (aromatic C), 129.3 (aromatic CH), 128.1 (aromatic CH), 86.5 (COCCO$_2$Et), 60.5 ($CO_2CH_2CH_3$), 48.1 (CH_2NH), 36.6 (CH_2C=C), 21.6 (CH_3Ar), 20.8 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); m/z (ES^+) 353 (MH^+, 34%), 182 (100); HRMS (ES^+) calcd for $C_{16}H_{21}N_2O_5S$ (MH^+) 353.1171, found 353.1166.

3.1.8. 3-Oxo-2-pyrrolidin-(2*E*)-ylidene-3-(2,2,2-trichloro-acetylamino)-propionic acid ethyl ester (15). To a stirred solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (63 mg, 0.4 mmol) was added trichloroacetyl isocyanate (48 μL, 0.4 mmol) and the mixture stirred for 18 h at 25 °C. The solvent was then removed in vacuo. The resulting yellow oil was purified by column chromatography (eluting with ethyl acetate/hexane 4:7) to give the *title compound* (R_f=0.25) (72 mg, 51%) as an off-white solid, mp 110–112 °C; ν_{max} (solution)/cm^{-1} 3197, 1750, 1664, 1614; δ_H (400 MHz; $CDCl_3$) 13.38 (1H, br s, Cl_3CCO–NH–CO), 11.31 (1H, br s, CH$_2$NH), 4.20 (2H, q, J 7.1, CO_2CH_2), 3.66 (2H, t, J 7.5, CH_2NH), 3.20 (2H, t, J 7.9, CH_2C=C), 2.04 (2H, apparent quintet, J 7.8, CH_2CH$_2$NH), 1.28 (3H, t, J 7.1, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 176.6 (Cl_3CCONH), 174.9 (CH_2CNH), 169.8 (ester C=O), 167.8 (NHCOC=C), 93.2 (Cl_3C), 87.8 (COCCO$_2$Et), 60.8 (CO_2CH_2), 48.4 (CH_2NH), 36.9 (CH_2C=C), 20.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); m/z (ES^+) 343 (MH^+, 18%) (+consistent isotopomer peaks), 182 (100); HRMS (ES^+) calcd for $C_{11}H_{14}N_2O_4{}^{35}Cl_3$ (MH^+) 343.0019, found 343.0015.

3.1.9. Phenylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (16). To a stirred solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (60 mg, 0.4 mmol) in $CHCl_3$ (6 mL) was added phenyl isothiocyanate (46 μL, 0.4 mmol), and the mixture stirred for 20 h under reflux. The solvent was removed in vacuo and the resulting brown solid recrystallised from aqueous ethanol to yield the *title compound* (65 mg, 58%) as colourless needles, mp 118–120 °C; ν_{max} (solution)/cm^{-1} 3176, 1649, 1248; δ_H (400 MHz; $CDCl_3$) 13.28 (1H, br s, CH$_2$NH), 12.47 (1H, br s, PhNH), 7.38 (2H, d, J 7.6, aromatic CH), 7.31 (2H, apparent t, J 7.9, aromatic CH), 7.16 (1H, t, J 7.4, aromatic CH), 4.18 (2H, q, J 7.2, CO_2CH_2), 3.64 (2H, t, J 7.4, CH_2NH), 3.15 (2H, t, J 7.8, CH_2C=C), 1.98 (2H, apparent quintet, J 7.6, CH_2CH$_2$NH), 1.28 (3H, t, J 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 190.2 (thioamide C=S), 174.1 (CH_2CNH), 170.2 (ester C=O), 139.7 (aromatic C), 128.6 (aromatic CH), 126.3 (aromatic CH), 126.2 (aromatic CH), 95.0 (CSCCO), 60.4 (CO_2CH_2), 48.0 (CH_2NH), 37.8 (CH_2C=C), 21.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); m/z (ES^+) 291 (MH^+, 29%), 198 (100); HRMS (ES^+) calcd for $C_{15}H_{19}N_2O_2S$ (MH^+) 291.1167, found 291.1172.

3.1.10. Benzylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (17). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (155 mg, 1 mmol) in $CHCl_3$ (6 mL) was added benzyl isothiocyanate (160 μL, 1.2 mmol), and the solution was stirred under reflux for 23 h. The mixture was allowed to cool, and the solvent was removed in vacuo. The resulting dark orange oil was purified by column chromatography (eluting with ethyl acetate/hexane 1:4) to give the *title compound* (R_f=0.41) (204 mg, 66%) as buff waxy solid, mp 83–87 °C; ν_{max} (solution)/cm^{-1} 3197, 1639, 1268; δ_H (400 MHz; $CDCl_3$) 13.05 (1H, br s, CH$_2$NH), 12.22 (1H, br s, PhCH$_2$NH), 7.18–7.11 (5H, m, aromatic CH), 4.79 (2H, apparent d, J 4.9, PhCH_2NH), 4.08 (2H, q, J 7.2, CO_2CH_2) 3.59 (2H, t, J 7.3, CH_2NH), 3.09 (2H, t, J 7.8, CH_2C=C), 1.93 (2H, apparent quintet, J 7.6, CH_2CH$_2$NH), 1.20 (3H, t, J 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 190.0 (thioamide C=S), 173.4 (CH_2CNH), 169.9 (ester C=O), 137.7 (aromatic C), 128.7 (aromatic CH), 127.9 (aromatic CH), 127.3 (aromatic CH), 94.3 (CSCCO$_2$Et), 60.1 (CO_2CH_2), 49.1 (PhCH_2NH), 47.8 (CH_2NH), 37.5 (CH_2C=C), 21.9 (CH_2CH_2NH), 14.4 ($CO_2CH_2CH_3$); m/z (ES^+) 305 (MH^+, 100%), 259 (24), 198 (78); HRMS (ES^+) calcd for $C_{16}H_{21}N_2O_2S$ (MH^+) 305.1324, found 305.1300.

3.1.11. *n*-Butylthiocarbamoyl-(2*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester (18). To a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (160 mg, 1.0 mmol) in pyridine (0.5 mL) was added butyl isothiocyanate (149 μL, 1.2 mmol). The solution was stirred at 100 °C in a sealed tube for 46 h, after which time the solvent was removed under reduced pressure. The resulting dark orange solid was recrystallised from aqueous ethanol to give the *title compound* (240 mg, 89%) as an orange solid, mp 53–56 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3176, 1633, 1257; δ_H (400 MHz; $CDCl_3$) 13.05 (1H, br s, CH$_2$NH), 10.92 (1H, br s, CH$_2$NHCS), 4.13 (2H, q, J 7.2, CO_2CH_2), 3.59 (2H, apparent q, J 7.3, CH_2NHCS), 3.58 (2H, t, J 7.3, CH_2NH), 3.08 (2H, t, J 7.8, CH_2C=C), 1.94 (2H, apparent quintet, J 7.6, CH_2CH$_2$NH), 1.58 (2H, apparent quintet, J 7.3, $CH_3CH_2CH_2$), 1.36 (2H, apparent sextet, J 7.4, $CH_3CH_2CH_2$), 1.24 (3H, t, J 7.2, $CO_2CH_2CH_3$), 0.88 (3H, t, J 7.3, $CH_3CH_2CH_2$); δ_C (100 MHz; $CDCl_3$) 189.5 (thiocarbamoyl C=S), 173.1 (CH_2CNH), 169.9 (ester C=O), 94.0 (CSCCO$_2$Et), 60.0 (CO_2CH_2), 47.6 (CH_2NH), 44.7 (CH_2NHCS), 37.4 (CH_2C=C), 30.3 ($CH_3CH_2CH_2$), 21.8 (CH_2CH_2NH), 20.4 ($CH_3CH_2CH_2$), 14.3 ($CO_2CH_2CH_3$), 13.8 ($CH_3CH_2CH_2$); m/z (APCI) 271 (MH^+, 74%), 225 (26), 198 (100), 156 (19); HRMS (ES^+) calcd for $C_{13}H_{23}N_2O_2S$ (MH^+) 271.1480, found 271.1476.

3.1.12. 2-Benzyl-3-oxo-1-thioxo-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carbothioic acid benzylamide (19). To a stirred suspension of sodium hydride (60% dispersion in oil, 18 mg, 0.44 mmol) in dry THF (10 mL), was added dropwise a solution of (*Z*)-pyrrolidin-2-ylidene-acetic acid ethyl ester **3** (62 mg, 0.4 mmol) in THF (5 mL) at 0 °C. The mixture was then stirred for 2 h at 25 °C. Benzyl isothiocyanate (53 μL, 1.0 mmol) was added, and the mixture stirred for 18 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (2×50 mL), dried over $MgSO_4$, and the solvent removed in vacuo. The resulting dark orange solid was purified by column chromatography

(eluting with ethyl acetate/hexane 3:7) to give, in order of elution, compound **17** (R_f=0.68) (46 mg, 38%) (data as above) and the *title compound* (R_f=0.45) (42 mg, 25%) as a pale solid, mp 130–132 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3337, 1664, 1288; δ_H (400 MHz; $CDCl_3$) 14.0 (1H, br s, $PhCH_2NHCS$), 7.45–7.05 (10H, m, aromatic CH), 6.45 (2H, s, one of $PhCH_2N$), 5.73 (2H, s, one of $PhCH_2N$), 3.74 (2H, t, *J* 7.4, CH_2NCS), 3.55 (2H, t, *J* 7.9, $CH_2C{=}C$), 2.17 (2H, apparent quintet, *J* 7.7, CH_2CH_2NCO); δ_C (100 MHz; $CDCl_3$) 191.0 (C=S), 183.4 (C=S), 176.6 (C=O), 157.8 (alkene C), 135.6 (aromatic C), 135.5 (aromatic C), 127.3 (aromatic CH), 127.2 (aromatic CH), 126.5 (aromatic CH), 126.1 (aromatic CH), 125.6 (aromatic CH), 125.6 (aromatic CH), 102.8 (alkene C), 56.0 (CH_2N), 50.5 (CH_2N), 47.9 (CH_2N), 37.1 (CH_2), 20.1 (CH_2); *m/z* (ES^+) 408 (MH^+, 100%), 383 (28), 303 (22), 238 (29), 182 (58); HRMS (ES^+) calcd for $C_{22}H_{22}N_3OS_2$ (MH^+) 408.1204, found 408.1208.

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