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An efficient synthesis of highly substituted pyrroles from β-oxodithiocarboxylates

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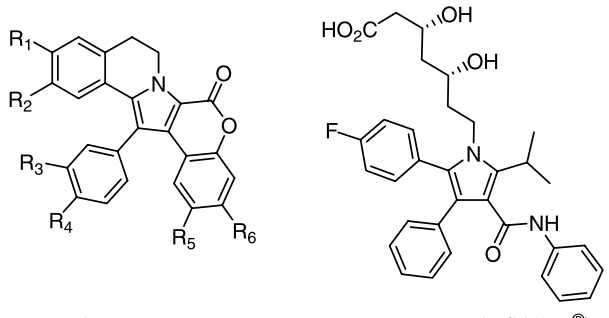
Abstract—α-Oxoketene-*N*,*S*-acetals, prepared by the reaction of alkyl glycinate hydrochlorides with β-oxodithiocarboxylates followed by alkylation, underwent cyclization in presence of chloromethyleneiminium salt derived from $POCl_3$/DMF to afford alkyl-3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates in excellent yields. Alkyl-3-aryl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates were formed in moderate yields when the same *N*,*S*-acetals were treated with DBU.

1. Introduction

Pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes.[1] Some of the recently isolated pyrrole containing marine natural products have been found to exhibit considerable cytotoxicity and function as multi drug resistant (MDR) reversal agents.[2] Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks having immense importance in material science.[3] The unique structural array and the unusual biological activity displayed by many pyrrole containing natural products have made them attractive synthetic targets. Classical methods like Knorr reaction, Paal–Knorr synthesis[4] and Hantzsh synthesis[5] are still widely in use for the synthesis of substituted pyrroles. Since these methods and more recent pyrrole syntheses[6] that showcase newer methodologies have limitations like functional group compatibility and regiospecificity, newer, simple and more convenient methods leading to highly substituted pyrroles are still desirable. In our recent communication, we have shown that α-oxoketene-*N*,*S*-acetals undergo cyclization in presence of Vilsmeier–Haack reagent to afford alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates in excellent yields. The utility of this method has been demonstrated by the formal total synthesis of the marine natural products lukianol A and lamellarin Q.[7]

β-Oxoketene-*N*,*S*-acetals are versatile building blocks widely used for heterocyclic synthesis.[8,9] In continuation of a research program directed towards the total synthesis of some pyrrole containing natural products like lamellarins[10] and the cholesterol lowering drug atorvastatin (Fig. 1),[11] we needed to develop an efficient method for the preparation of highly functionalized pyrroles.



lamellarins atorvastatin (Lipitor®)

Figure 1.

We envisioned that appropriately substituted ketene-*N*,*S*-acetals, prepared by the reaction of dithiocarboxylates with alkyl glycinate followed by alkylation, could be transformed into the corresponding pyrrole derivatives. Herein we

Keywords: Pyrroles; Dithiocarboxylates; Ketene-*N*,*S*-acetals; Vilsmeier–Haack reagent.
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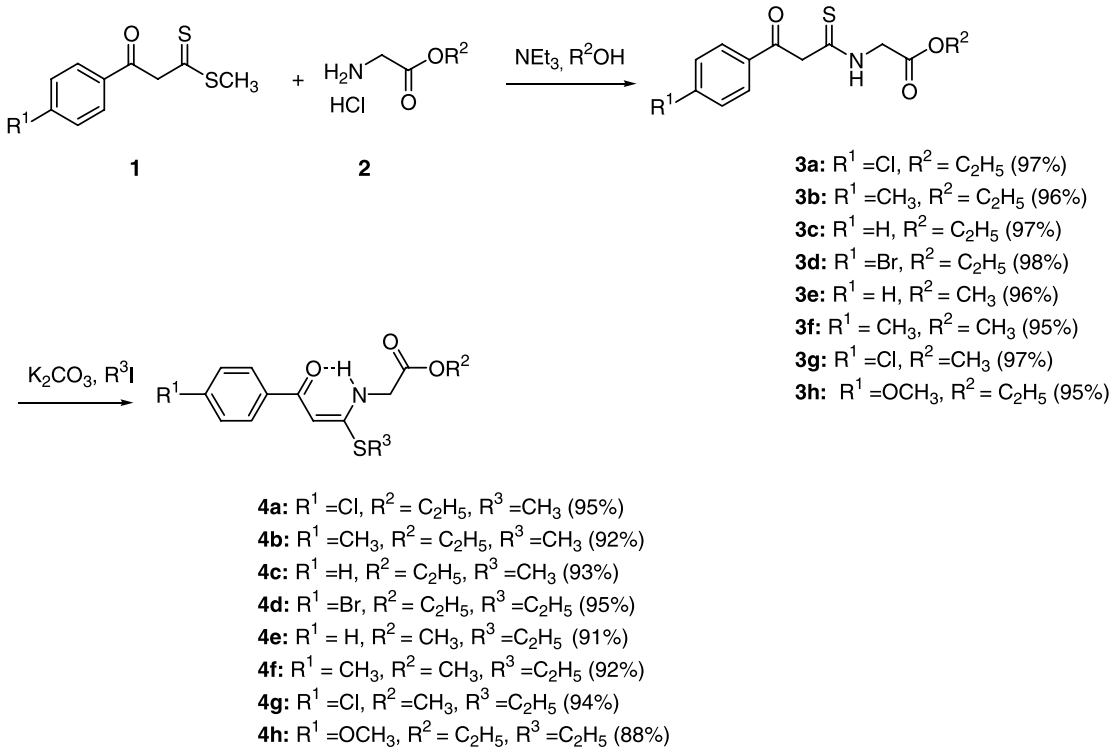
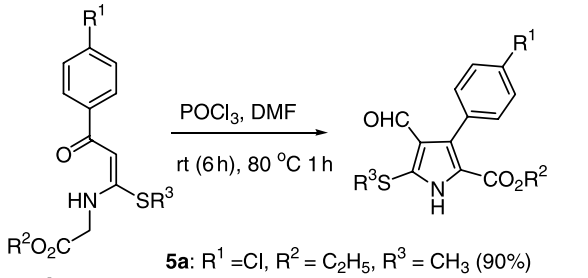


Scheme 1.

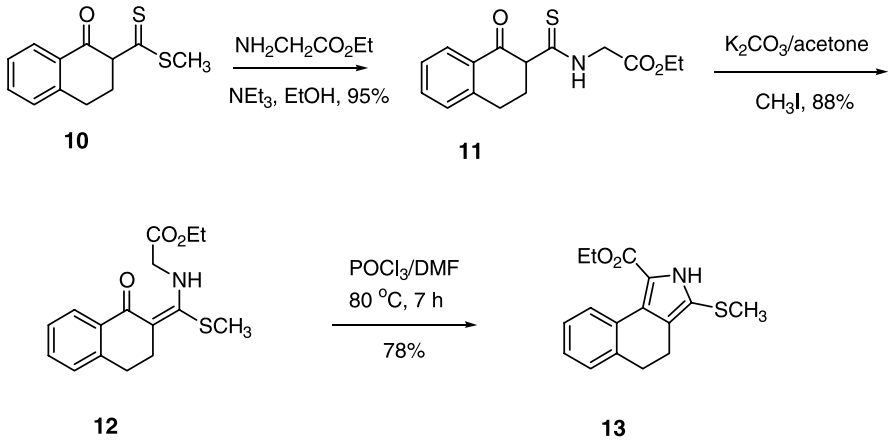
present a facile and high yielding regioselective method for synthesizing 2,3,4,5-tetra and 2,3,5-tri substituted pyrroles from readily available inexpensive starting materials by a simple sequence of reactions. The key step in this method is the iminium salt or base catalyzed cyclization of α-oxoketene-*N*,*S*-acetals **4**.

2. Results and discussion

Dithiocarboxylates **1**, prepared[12] by the condensation of enolates of active methylene ketones with dialkyl trithiocarbonates, are valuable multifunctional synthetic intermediates.[13,14] They are also used as precursors for α-oxoketene dithioacetals, α-oxoketene-*N*,*S*-acetals and α-oxoketene-*O*,*S*-acetals.[15] Reaction of enolizable carbonyl compounds with dialkyl trithiocarbonates in DMF using sodium hydride as base afforded β-oxodithiocarboxylates **1** in excellent yields within 1 h at room temperature. Treatment of the dithiocarboxylates **1** with ethyl glycinate in absolute alcohol in presence of triethyl amine at room temperature gave the thioamide **3** in nearly quatitative yields. The ^{1}H NMR spectrum of thioamide **3** in $CDCl_3$ shows two sets of peaks corresponding to the keto and enol forms. The thioamides **3** underwent facile alkylation in presence of potassium carbonate using alkyl iodide in acetone to give the *N*,*S*-acetal **4** in good yield. (Scheme 1). The ketene-*N*,*S*-acetals **4** thus generated were unstable in strongly basic medium and intractable mixture of products were formed during their attempted base catalyzed cyclization. However, in the presence of Vilsmeier–Haack reagent,[16] prepared from $POCl_3$ and DMF, they underwent iminoalkylation followed by intramolecular cyclization to afford substituted pyrroles **5** (Scheme 2). Interestingly the carbonyl group of the aroyl group rather than the iminium moiety was involved in the cyclization. Attempts to cyclize the *N*,*S*-acetal in presence of $POCl_3$ in THF or in the presence of other Lewis acid catalysts did not afford any cyclization product. When cyclization of the ketene *N*,*S*-acetals **4** was attempted by refluxing it in glacial acetic acid, partial

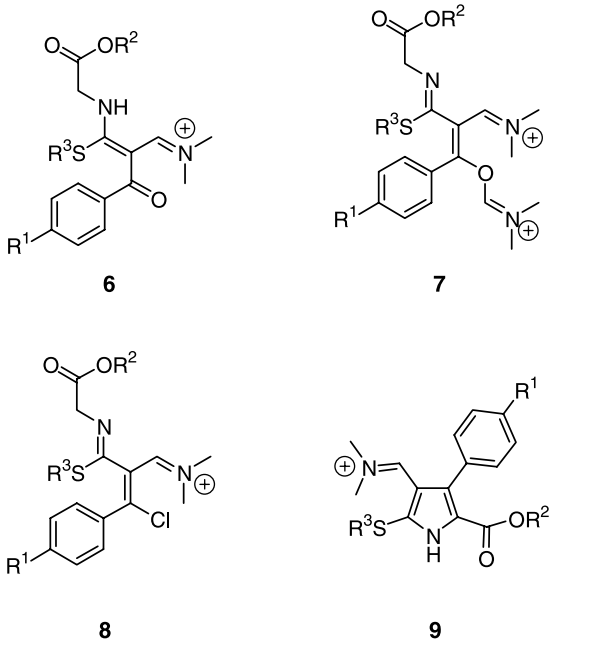


Scheme 2.



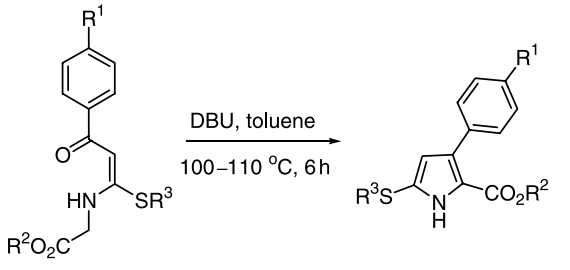
Scheme 3.

hydrolysis takes place leading to the formation of corresponding β-oxothiolesters.



The formation of pyrrole carbaldehydes **5** can be rationalized as follows. Sequential iminoalkylations of the ketene-*N*,*S*-acetal moiety and the enaminoketone functionality leads to the intermediate **6** and **7**, respectively. The chlorovinyl iminium salt **8** can be obtained by the displacement of *N*,*N*-dimethyl formamide by chloride ion from **7**. Cyclization of **8**, involving the imino acetate group and the chlorovinyl iminium moiety, leads to the formation of iminium salt **9**, which affords the pyrrole **5** on hydrolysis. The electron withdrawing nature of iminium salt moiety in **6** serve to increase the overall yields as it facilitates the cyclization. Vilsmeier–Haack reactions of β-oxodithiocarboxylates are known to afford β-chloro, β-methylthio α,β-unsaturated ketones.[17] Our efforts to synthesize pyrroles directly from thioamide **3** under Vilsmeier condition afforded complex product mixtures containing *N*,*N*-dimethylamino substituted pyrroles. Functionalized ketene-*N*,*S*-acetal **12** derived from cyclic carbonyl compounds like α-tetralone, which cannot iminoalkylate also underwent cyclization under Vilsmeier–Haack conditions to afford the annulated pyrrole **13** in 78% yield after heating at 80 °C for 7 h (Scheme 3).

Cyclization of the ketene *N*,*S*-acetals **4** was also examined under non nucleophilic bases. When **4** was heated in toluene in presence of DBU at 100–110 °C trisubstituted pyrroles **14** was formed in moderate yields (Scheme 4). The yield of **14** could be increased by adding DBU in three portions in equal intervals. The structure of **14** was confirmed on the basis of spectral and analytical data. In ^{1}H NMR, the single proton on the pyrrole ring appeared as a doublet at δ 6.39 (J= 3 Hz) ppm due to long range coupling with NH proton. Annulated pyrrole **13** was also formed in 56% yield when the *N*,*S*-acetal **12** derived from tetralone was heated in the presence of DBU for 8 h.



14a: R^1 = Cl, R^2 = CH_3, R^3 = C_2H_5 (34%)
14b: R^1 =H, R^2 = C_2H_5, R^3 = C_2H_5 (45%)
14c: R^1 = Cl, R^2 =C_2H_5, R^3 = CH_3 (32%)
14d: R^1 =Br, R^2 = C_2H_5, R^3 = C_2H_5 (28%)
14e: R^1 =CH_3, R^2 = CH_3, R^3 = CH_3 (24%)

Scheme 4.

In summary, we have developed straightforward and simple methods for the regiocontrolled formation of tetra and trisubstitued pyrroles starting from readily available and inexpensive dithioesters and glycine esters. The substitution pattern can be selectively tuned by the use of appropriately functionalized ketene-*N*,*S*-acetals. As an illustrative example, we have extended the scope of the cyclization procedure for the synthesis of a benzannulated isoindole ring system. The removable alkyl sulphanyl group present

on the pyrrole ring can extend the scope of this method for the synthesis of indoles, thienopyrroles, pyrridinopyrroles as well as isoquoline annulated pyrroles found in various natural products.

3. Experimental

3.1. General

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. Infrared spectra were recorded on Shimadzu JASCO FT/IR-5300 or ABB Bomem 104 spectrometer. Proton NMR spectra were recorded on a Bruker DRX-300 (300 MHz) spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million downfield from internal tetramethyl silane. Coupling constants J are given in Hertz. Mass spectra (EIMS) were obtained on a Finngen-Mat 312 instrument. Elemental analyses were recorded on an elementar vario EL III analyzer.

3.2. General procedure for the synthesis of dithio esters (1)

Sodium hydride (50% suspension in mineral oil, 0.96 g, 20 mmol) was washed with anhydrous petroleum ether and suspended in ice cooled anhydrous DMF (10 ml). To this was added the appropriate ketone (10 mmol) and stirred for 1 h, allowing the mixture to attain room temperature during this period. The reaction mixture was then poured over crushed ice (100 g) and extracted with diethyl ether (3× 50 mL). The organic layer was washed with water and dried using anhydrous Na_2SO_4. The solvent was removed in vacuum and the crude product was purified by passing through a short column of silica gel using hexane. The dithioesters prepared were characterized by comparing the spectral and physical data with reported values.[12]

3.3. General procedure for the synthesis of β-oxothio amides (3a–h)

Triethylamine (20 mmol) was added to a mixture of β-oxodithioester **1** (10 mmol) and glycine ester hydrochloride **2** (10 mmol) in appropriate dry alcohol (20 mL) at room temperature. After stirring for 4 h at room temperature the reaction mixture was poured into 100 mL of ice cold water. The reaction mixture was extracted with chloroform (3×50 mL), washed with water (2×25 mL), dried (Na_2SO_4) and evaporated to afford the crude product **3**, which were purified by recrystalizing from hexane–ethyl acetate (7/3).

3.3.1. Ethyl 2-{[3-(4-chlorophenyl)-3-oxopropanthioyl]-amino}acetate (3a). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.45 g, 10 mmol) with glycine ethylester hydrochloride (10 mmol) in ethanol. Yield 2.90 g (97%), mp 87–88 °C. IR (KBr) ν_{max}=3291, 1727, 1611, 1537, 1210, 1094, 818, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 1.32 ppm (t, 3H, J=7 Hz, OCH_2CH_3), 4.28 (m, 2H, OCH_2CH_3, keto and enol forms), δ 4.40 (d, 0.8H, J=4 Hz, NCH_2, enol form), δ 4.42 (d, 1.2H, J=4 Hz, NCH_2, keto form), δ 4.50 (s, 1.2H, methylene, keto form), 6.05 (s, 0.4H, vinylic, enol form), δ 7.39 (d, 0.4H, J=8 Hz, aromatic), δ 7.47 (d, 1H, J=8 Hz, aromatic+0.4H, N*H*, enol form), δ 7.72 (d, 0.4H, J=8 Hz, aromatic), 7.98 (d, 0.6H, J=8 Hz, aromatic), 9.50 (br s, 0.6H, NH, keto form) 14.36 (s, 0.4H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$)[18] δ=14.5, 48.1, 53.1, 62.5, 127.7, 129.6, 130.6, 141.2, 168.8, 192.1, 194.9. EIMS *m/z* (%) 301 (M^++2, 7), 299 (M^+, 18), 266 (12), 181 (17), 139 (100), 111 (54). Anal. Calcd for $C_{13}H_{14}ClNO_3S$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.15; H, 4.64; N, 4.71.

3.3.2. Ethyl 2-{[3-(4-methylphenyl)-3-oxopropanthioyl]-amino}acetate (3b). Obtained as pale yellow needles by the reaction of methyl 3-(4-methylphenyl)-3-oxopropanedithioate (2.24 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 2.60 g (96%), mp 120–121 °C. IR (KBr) ν_{max}=3316, 1751, 1668, 1535, 1218, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 1.31 (t, 3H, J=7 Hz, CH_2CH_3), 2.42 (s, 3H, CH_3), 4.28 (q, 2H, J=7 Hz, CH_2CH_3), 4.41 (d, 0.6H, J=4 Hz, NCH_2, enol form), 4.44 (d, 1.4H, J=4 Hz, NCH_2, keto form), 4.51 (s, 1.4H, methylene, keto form), 6.08 (s, 0.3H, vinylic, enol form), 7.22 (d, 0.6H, J=8 Hz, aromatic) 7.28 (d, 1.4H, J=8 Hz, aromatic), 7.68 (d, 0.6H, J=8 Hz, aromatic) 7.93 (d, 1.4H, J=8 Hz, aromatic+0.3H, N*H*, enol form), 9.81 (br s, 0.7H, NH, keto form), 14.36 (s, 0.3H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 22.1, 48.1, 52.5, 62.5, 126.4, 129.2, 133.7, 145.8, 168.8, 192.3, 196.0. EIMS *m/z* (%) 279 (M^+, 22), 246 (15), 177 (12), 148 (13), 119 (100), 91 (54). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.07; H, 6.18; N, 5.12.

3.3.3. Ethyl 2-[(3-oxo-3-phenylpropanthioyl)amino]-acetate (3c). Obtained as pale yellow needles by the reaction of methyl 3-oxo-3-phenylpropanedithioate (2.1 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 2.5 g (97%), mp 82–83 °C. IR (KBr) ν_{max}=3292, 1724, 1609, 1538, 1208, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 1.33 (t, 3H, J=7 Hz, CH_2CH_3), 4.28 (q, 2H, J=7 Hz, CH_2CH_3), 4.41 (d, 0.6H, J=4 Hz, NCH_2, enol form), 4.45 (d, 1.4H, J=4 Hz, NCH_2, keto form), 4.54 (s, 1.4H, methylene, keto form), 6.10 (s, 0.3H, vinylic, enol form), 7.36–8.04 (m, 5.6H, aromatic+0.3 N*H* enol form), 9.66 (br s, 0.7H, N*H*, keto form), 14.35 (s, 0.3H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.0, 47.7, 52.4, 61.9, 126.4, 128.8, 134.2, 135.7, 168.4, 192.3, 195.8. EIMS *m/z* (%) 265 (M^+, 97), 232 (51), 163 (11), 121 (35), 105 (100). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.76; H, 5.61; N, 5.42.

3.3.4. Ethyl 2-{[3-(4-bromophenyl)-3-oxopropanthioyl]-amino}acetate (3d). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.80 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 3.30 g (98%), mp 88–90 °C. IR (KBr) ν_{max}=3293, 1716, 1609, 1537, 1208, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 1.32 ppm (t, 3H, J=7 Hz, OCH_2CH_3), 4.28 (m, 2H, OCH_2CH_3, keto and enol forms), δ 4.40 (d, 0.8H, J=4 Hz, NCH_2, enol form), δ 4.43 (d, 1.2H, J=4 Hz, NCH_2, keto form), δ 4.49 (s, 1.2H, methylene, keto form), 6.05 (s, 0.4H, vinylic, enol form), δ 7.37 (br s, 0.6H, N*H*, keto form), δ 7.54 (d, 0.6H, J=8 Hz, aromatic), δ 7.64 (d, 2.8H, J=8 Hz, aromatic), δ 7.91 (d, 0.6H, J=8 Hz, aromatic), 9.49 (br s, 0.4H, N*H*, enol form),

14.35 (s, 0.4H, O*H*, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 48.1, 52.9, 62.5, 127.9, 130.6, 132.6, 134.4, 168.6, 192.1, 195.2. EIMS *m/z* (%) 345 (M^++2, 22), 343 (M^+, 22), 312 (16), 243 (8), 183 (100), 155 (52) and 102 (12). Anal. Calcd for $C_{13}H_{14}BrNO_3S$: C, 45.36; H, 4.10; N, 4.07. Found: C, 45.44; H, 4.02; N, 4.21.

3.3.5. Methyl 2-[(3-oxo-3-phenylpropanthioyl)amino]-acetate (3e). Obtained as pale yellow needles by the reaction of ethyl 3-oxo-3-phenylpropanedithioate (2.10 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.40 g (96%), mp 90–92 °C. IR (KBr) ν_{max}=3301, 1726, 1609, 1537, 1211, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 3.82 (s, 2.1H, OCH_3 keto form), 3.84 (s, 0.9H, OCH_3, enol form), 4.44 (d, 0.6H, J=3 Hz, NCH_2 enol form), 4.48 (d, 1.4H, J=3 Hz, NCH_2 keto form), 4.55 (s, 1.4H, methylene, keto form), 6.09 (s, 0.3H, vinylic, enol form), 7.42–7.80 (m, 4.4H, aromatic+N*H* 0.3, keto form), 8.79 (d, 0.9H, J=8 Hz, aromatic), 9.72 (br s, 0.7H, N*H*, enol form), 14.35 (s, 0.3H, O*H*, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=45.4, 47.9, 52.8, 126.4, 129.2, 131.4, 136.2, 169.3, 192.3, 196.4. EIMS *m/z* (%) 251 (M^+, 26), 236 (12), 187 (18), 149 (13), 105 (100) and 97 (44). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.46; H, 5.12; N, 5.68.

3.3.6. Methyl 2-{[3-(4-methylphenyl)-3-oxopropanthioyl]-amino}acetate (3f). Obtained as pale yellow needles by the reaction of methyl 3-(4-methylphenyl)3-oxopropanedithioate (2.24 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.5 g (95%), mp 110–111 °C. IR (KBr) ν_{max}=3314, 1726, 1611, 1211, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=3:1; δ 2.39 (s, 0.75H, ArCH_3, enol form), 2.42 (s, 2.25H, ArCH_3, keto form), 3.82 (s, 3H, OCH_3), 4.43 (d, 0.5H, J=4 Hz, NCH_2, enol form), 4.45 (d, 1.5H, J=4 Hz, NCH_2, keto form), 4.52 (s, 1.5H, methylene, keto form), 6.10 (s, 0.25H, methyne, enol form), 7.22 (d, 0.5H, J=8 Hz, aromatic), 7.34 (d, 1.5H, J=8 Hz, aromatic), 7.68 (d, 0.5H, J=8 Hz, aromatic), 7.93 (1.5H, J=8 Hz, aromatic), 7.35 (br s, 0.75H, N*H*, keto form), 9.79 (br s, 0.25H, N*H*, enol form), 14.33 (s, 0.25H, O*H* enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=21.1, 45.5, 47.9, 52.4, 129.2, 130.0, 133.7, 145.8, 169.2, 189.3, 196.0. EIMS *m/z* (%) 265 (M^+, 44), 232 (18), 204 (17), 177 (14), 144 (15), 119 (100) and (105). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.94; H, 5.62; N, 5.19.

3.3.7. Methyl 2-{[3-(4-chlorophenyl)-3-oxopropanthioyl]-amino}acetate (3g). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.45 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.7 g (97%), mp 80–81 °C. IR (KBr) ν_{max}=3340, 1736, 1611, 1513, 1204, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 3.80 (s, 1.8H, OCH_3, keto form), 3.81 (s, 1.2H, OCH_3, enol form), 4.42 (d, 0.8H, J=4.8 Hz, NCH_2, enol form), 4.45 (d, 1.2H, J=4 Hz, NCH_2, keto form), 4.50 (s, 1.2H, methylene, keto form), 6.09 (s, 0.4H, methyne, enol form), 7.36 (d, 0.8H, J=8 Hz, aromatic) 7.44 (d, 1.2H, J=8 Hz, aromatic), 7.68 (d, 0.8H, J=8.7 Hz, aromatic), 7.95 (d, 1.2H, J=8 Hz, aromatic), 9.51 (br s, 0.6H, N*H*, enol form), 14.31 (s, 0.4H, enol, O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=45.7, 47.9, 53.1, 127.7, 129.6, 137.4, 141.3, 169.35, 192.2, 195.0. EIMS *m/z* (%) 287 (M^++2, 5), 285 (M^+, 16), 224 (18), 141 (24), 139 (100) and 111 (64). Anal. Calcd for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; N, 4.90. Found: C, 50.33; H, 4.34; N, 4.84.

3.3.8. Ethyl 2-{[3-(4-methoxyphenyl)-3-oxopropanthioyl]-amino}acetate (3h). Obtained as pale yellow needles by the reaction of ethyl 3-(4-methoxyphenyl)-3-oxopropane dithioate (2.4 g, 10 mmol) with glycine ethyl ester hydrochloride in ethanol. Yield 2.8 g (95%), mp 84–86 °C. IR (KBr) ν_{max}=3304, 1722, 1608, 1537, 1209, 771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto form only δ 1.31 (t, 3H, J=6 Hz, OCH_2CH_3), 3.88 (s, 3H, ArOCH_3), 4.27 (q, 2H, J=6 Hz, CH_2CH_3), 4.44 (d, 2H, J=4 Hz, NCH_2), 4.48 (s, 2H, methylene), 6.94 (d, 2H, J=9 Hz, aromatic), 8.02 (d, 2H, J=9 Hz, aromatic), 9.81 (br s, 1H, N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 48.1, 52.4, 55.9, 62.2, 114.4, 129.1, 131.6, 164.8, 168.8, 194.7, 196.2. EIMS *m/z* (%) 295 (M^+, 34), 262 (15), 135 (100) and 121 (24). Anal. Calcd for $C_{14}H_{17}ClNO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.84; H, 5.89; N, 4.85.

3.3.9. Ethyl 2-{[(1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)carbothioyl]amino}acetate (11). Obtained as white needles by the reaction of methyl 1-oxo-1,2,3,4-tetrahydro-2-naphthalene-carbodithioate (2.3 g, 10 mmol) with glycine ethyl ester hydrochloride in ethanol. Yield 2.7 g (95%), mp 62–64 °C. IR (KBr) ν_{max}=3499, 3207, 1738, 1680, 1548, 1224, 785, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=4:1; δ 1.29 (m, 3H, OCH_2CH_3, keto and enol forms), 2.68 (m, 2H, CH_2CH_2, keto and enol forms) 2.89 (m, 0.4H, CH_2CH_2, enol form), 3.05 (m, 0.8H, CH_2CH_2, keto form), 3.17 (m, 0.8H, CH_2CH_2, keto form), 3.76 (t, 0.8H, J=7 Hz, C*H*, keto form), 4.43 (m, 4H, OCH_2CH_3 and NCH_2, keto and enol forms), 6.16 (d, 0.2H, J=8 Hz, aromatic, enol form), 7.23–8.02 (m, 2.8H, aromatic, keto and enol forms), 7.90 (d, 0.2H, J=8 Hz, aromatic, enol form), 8.01 (d, 0.8H, J=8 Hz, aromatic, keto form), 9.27 (br s, 1H, N*H*), 14.76 (s, 0.2H, O*H*, enol). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 28.7, 30.1, 48.1, 59.6, 62.4, 127.2, 128.3, 129.1, 132.2, 134.6, 144.7, 169.1, 196.3, 200.6. EIMS *m/z* (%) 291 (M^+, 64), 273 (18), 240 (17), 187 (24), 145 (100), 128 (54), 115 (84) and 115 (34). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.95; H, 5.74; N, 4.89.

3.4. General procedure for the synthesis of alkyl 2-{[(*E*)-3-aryl-1-(alkylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4)

A suspension of the thioamide **3** (10 mmol) and anhydrous K_2CO_3 (3 g, 20 mmol) in dry acetone (30 ml) was refluxed with stirring for 30 min. The mixture was cooled and alkyl iodide (20 mmol) was added and again stirred at room temperature for 3 h. When the reaction was completed (TLC), the mixture was poured into ice-cold water (100 mL) and extracted using dichloromethane (2×50 mL). The organic layer was washed with water (2×100 mL) and dried using anhydrous Na_2SO_4. Evaporation of the solvent afforded a yellow glass, which solidifies on standing. Recrystallisation of the crude product from hexane–ethyl acetate (7/3) afforded title compound **4** in 88–95% yields.

3.4.1. Ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4a). Obtained

as yellow prisms by the methylation of ethyl 2-{[(3-4-chlorophenyl)-3-oxopropanthioyl]amino}acetate **3a** (2.60 g, 10 mmol) using methyl iodide. Yield 2.90 g (95%), mp 96–98 °C. IR (KBr) ν_{max}=3072, 1744, 1559, 1533, 1470, 1203, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7 Hz, CH_2CH_3), 2.49 (s, 3H, SCH_3), 4.17 (d, 2H, J=5 Hz, NCH_2), 4.27 (q, 2H, J=7 Hz, CH_2CH_3), 5.68 (s, 1H, vinylic), 7.37 (d, 2H, J=8 Hz, aromatic), 7.80 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 14.9, 45.8, 62.2, 87.8, 128.2, 128.8, 137.1, 139.1, 168.8, 169.5, 184.9. EIMS *m/z* (%) 315 (M^++2), 313 (M^+, 23), 266 (36), 238 (25), 181 (24), 139 (100), 111 (43). Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.58; H, 5.14; N, 4.46. Found: C, 53.74; H, 5.03; N, 4.32.

3.4.2. Ethyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4b). Obtained as yellow prisms by the methylation of ethyl 2-{[(3-4-methylphenyl)-3-oxopropanthioyl]amino}acetate **3b** (2.70 g, 10 mmol) using methyl iodide. Yield 2.70 g (92%), mp 110–111 °C. IR (KBr) ν_{max}=2994, 1744, 1588, 1544, 1210, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7 Hz, CH_2CH_3), 2.37 (s, 3H, $ArCH_3$), 2.42 (s, 3H, SCH_3), 4.15 (d, 2H, J=5 Hz, NCH_2), 4.25 (q, 2H, J=7 Hz, OCH_2CH_3), 5.72 (s, 1H, vinylic), 7.2 (d, 2H, J=8 Hz, aromatic), 7.78 (d, 2H, J=8 Hz, aromatic), 11.96 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=14.5, 14.9, 21.8, 45.8, 62.1, 88.0, 127.5, 129.3, 138.0, 141.4, 168.7, 168.9, 186.3. EIMS *m/z* (%) 293 (M^+, 27), 246 (37), 218 (15), 172 (19), 161 (14), 119 (100) and 91 (52). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.28; H, 6.65; N, 4.62.

3.4.3. Ethyl 2-{[(*E*)-1-(methylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate (4c). Obtained as yellow prisms by the methylation of ethyl 2-[(3-oxo-3-phenylpropanthioyl)-amino]acetate **3c** (2.7 g, 10 mmol) using methyl iodide. Yield 2.6 g (93%), mp 90–92 °C. IR (KBr) ν_{max}=3074, 1745, 15568, 1523, 1205, 727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7 Hz, OCH_2CH_3), 2.48 (s, 3H, SCH_3), 4.17 (d, 2H, J=5 Hz, NCH_2), 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.73 (s, 1H, vinylic), 7.36–7.45 (m, 3H, aromatic), 7.85–7.89 (dd, 2H, aromatic), 11.98 (br s, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 14.9, 45.8, 62.1, 88.2, 127.8, 128.6, 131.1, 140.7, 168.9, 169.1, 186.4. EIMS *m/z* (%) 279 (M^+, 17), 232 (35), 204 (15), 176 (8), 147 (24) and 105 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.07; H, 6.26; N, 4.87.

3.4.4. Ethyl 2-{[(*E*)-3-(4-bromophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4d). Obtained as yellow prisms by the ethylation of ethyl 2-{[(3-4-bromophenyl)-3-oxopropanthioyl]amino}acetate **3d** (3.40 g, 10 mmol) using ethyl iodide. Yield 3.50 g (95%), mp 97–98 °C. IR (KBr) ν_{max}=3093, 1750, 1587, 1526, 1210, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7 Hz, SCH_2CH_3), 1.42 (t, 3H, J=7 Hz, OCH_2CH_3), 3.02 (q, 2H, J=7 Hz, SCH_2CH_3), 4.17 (d, 2H, J=3 Hz, NCH_2) 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.73 (s, 1H, vinylic), 7.53 (d, 2H, J=8 Hz, aromatic), 7.72 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, –NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.9, 14.5, 26.5, 45.8, 62.1, 88.5, 125.5, 129.0, 131.7, 139.6, 168.7, 168.8, 184.9. EIMS *m/z* (%) 373 (M^++2, 18), 371 (M^+, 17), 345 (15), 310 (19), 282 (14), 183 (100), 157 (42) and 102 (11). Anal. Calcd for $C_{15}H_{18}BrNO_3S$: C, 48.39; H, 4.87; N, 3.76. Found: C, 48.22; H, 5.97; N, 3.96.

3.4.5. Methyl 2-{[(*E*)-1-(ethylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate (4e). Obtained as yellow prisms by the ethylation of methyl 2-[(3-oxo-3-phenylpropanthioyl)-amino]acetate **3e** (2.50 g, 10 mmol) using ethyl iodide as a yellow glass. Yield 2.40 g (91%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, J=7 Hz, SCH_2CH_3), 3.80 (s, 3H, OCH_3), 3.01 (q, 2H, J=7 Hz, SCH_2CH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.37–7.44 (m, 3H, aromatic), 7.83–7.88 (m, 2H, aromatic), 12.09 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.8, 15.3, 46.0, 54.3, 88.6, 126.7, 129.2, 130.5, 136.3, 169.1, 171.4, 185.9. EIMS *m/z* (%) 279 (M^+, 22), 251 (17), 218 (23), 190 (28), 158 (14) and 105 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.05; H, 6.23; N, 5.15.

3.4.6. Methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4f). Obtained as yellow prisms by the ethylation of methyl 2-{[(3-4-methylphenyl)-3-oxopropanthioyl]amino}acetate **3f** (2.60 g, 10 mmol) using ethyl iodide. Yield 2.70 g (92%), mp 90–91 °C. IR (KBr) ν_{max}=2932, 1742, 1589, 1555, 1243, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, J=7 Hz, SCH_2CH_3), 2.38 (s, 3H, $ArCH_3$), 3.79 (s, 3H, OCH_3), 3.00 (q, 2H, J=7 Hz, SCH_2CH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.20 (d, 2H, J=8 Hz, aromatic), 7.76 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.4, 21.3, 26.1, 45.2, 52.5, 88.5, 127.0, 128.8, 137.5, 140.9, 167.3, 169.0, 185.9. EIMS *m/z* (%) 293 (M^+, 27), 265 (15), 232 (39), 172 (8), 119 (100) and 105 (12). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.28; H, 6.45; N, 4.92.

3.4.7. Methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4g). Obtained yellow prisms by the ethylation of methyl 2-{[(3-4-chlorophenyl)-3-oxopropanthioyl]amino}acetate **3g** (2.80 g, 10 mmol) using ethyl iodide. Yield 3 g (94%), mp 94–95 °C. ν_{max}=3063, 2965, 1744, 1575, 1285, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7 Hz, SCH_2CH_3), 3.02 (q, 2H, J=7 Hz, SCH_2CH_3), 3.80 (s, 3H, OCH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.20 (d, 2H, J=8 Hz, aromatic), 7.76 (d, 2H, J=8 Hz, aromatic), 12.02 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.8, 26.5, 45.7, 52.0, 88.6, 128.3, 128.8, 137.1, 139.0, 168.6, 169.3, 184.9. EIMS *m/z* (%) 315 (M^++2, 9), 313 (M^+, 28) 285 (14), 252 (32), 224 (30), 192 (7), 139 (100) and 115 (42). Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.58; H, 5.14; N, 4.46. Found: C, 53.45; H, 5.25; N, 4.34.

3.4.8. Ethyl 2-{[(*E*)-1-(ethylsulfanyl)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]amino}acetate (4h). Obtained as yellow prisms by the ethylation of ethyl 2-{[3-(4-methoxyphenyl)-3-oxopropanthioyl]amino}acetate **3h** (2.90 g, 10 mmol) using ethyl iodide. Yield 2.8 g (88%), mp 105–106 °C. IR (KBr) ν_{max}=3085, 1748, 1521, 1466, 1245, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7 Hz, SCH_2CH_3), 1.41 (t, 3H, J=7 Hz, OCH_2CH_3), 3.01 (q, 2H, J=7 Hz, SCH_2CH_3), 3.84 (s, 3H, $ArOCH_3$), 4.17 (d, 2H, J=3 Hz, NCH_2) 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.77 (s, 1H, vinylic), 6.90 (d, 2H, J=8 Hz, aromatic), 7.85

(d, 2H, $J=8$ Hz, aromatic), 11.92 (br s, 1H, –N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=13.9$, 14.5, 26.5, 45.8, 55.6, 62.0, 88.6, 113.7, 129.2, 133.3, 162.1, 167.3, 169.1, 185.6. EIMS *m/z* (%) 323 (M^+, 17), 262 (25), 234 (9), 188 (18), 135 (100) and 121 (22). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.57; H, 6.39; N, 4.43.

3.4.9. Ethyl 2-({methylsulfanyl)[1-oxo-3,4-dihydro-2(1*H*)-naphthalenyliden]amino}acetate (12). Obtained as white prisms by the methylation of ethyl 2-{[(1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)carbothioyl]amino}acetate **11** (2.90 g, 10 mmol) using methyl iodide. Yield 2.8 g (88%), mp 132–134 °C. IR (KBr) $\nu_{max}=2986$, 1736, 1315, 1022, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.33 (s, 3H, SCH_3), 2.86 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 4.27 (q, 2H, $J=7$ Hz, OCH_2CH_3), 4.33 (s, 2H, NCH_2), 7.26–7.38 (m, 3H, aromatic), 8.08 (d, 1H, $J=8$ Hz, aromatic), 13.40 (br s, N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 18.0, 27.7, 29.9, 47.3, 61.8, 108.0, 126.9, 127.3, 127.7, 131.7, 135.9, 142.1, 162.4, 170.4, 186.1. EIMS *m/z* (%) 305 (M^+, 24), 258 (78), 228 (23), 184 (72), 173 (100), 128 (58), 115 (92) and 105 (34). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.78; H, 6.37; N, 4.42.

3.5. General procedure for the synthesis of alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates (5)

Vilsmeier reagent was prepared by mixing ice cold, dry DMF (25 mL) and $POCl_3$ (2 mL, 20 mmol). The mixture was then stirred for 30 min at room temperature. The *N*,*S*-acetal **4** (3.25 g, 10 mmol) was dissolved in dry DMF (10 mL) and added to the Vilsmeier reagent keeping the temperature at 0–5 °C. The reaction mixture was stirred for 6 h at room temperature, heated to 80 °C for 1 h with stirring and was cooled and poured into cold, aqueous saturated K_2CO_3 (200 mL). It was then extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford the crude product, which was chromatographed over silica gel using hexane–ethylacetate (4/1) as eluent to give alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates **5**.

3.5.1. Ethyl 3-(4-chlorophenyl)-4-formyl-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (5a). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4a** (3.13 g, 10 mmol) as colorless plates. Yield 2.91 g (90%), mp 118–119 °C. IR (KBr) $\nu_{max}=3234$, 1660, 1539, 1249, 1170, 1018, 835, 794, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.62 (s, 3H, SCH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.33 (d, 2H, $J=8$ Hz, aromatic), 7.38 (d, 2H, $J=8$ Hz, aromatic) 9.43 (br s, 1H, N*H*), 9.62 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.3$, 15.5, 61.3, 120.7, 123.0, 128.2, 130.4, 132.2, 133.7, 134.4, 138.9, 160.8, 186.3; EI-MS *m/z* (%)= 325 ($M^+ +2$, 39) 323 (M^+, 100), 276 (38), 244 (20), 216 (42), 179 (20), 161 (5), 113 (3). Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33. Found: C, 55.50; H, 4.48; N, 4.42.

3.5.2. Ethyl 4-formyl-3-(4-methylphenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (5b). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4b** (2.93 g, 10 mmol) as colorless plates. Yield 2.60 g (87%), mp 108–109 °C. IR (KBr) $\nu_{max}=3378$, 1670, 1640, 1233, 1162, 1020, 799, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 2.61 (s, 3H, SCH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.20 (d, 2H, $J=8$ Hz, aromatic), 7.29 (d, 2H, $J=8$ Hz, aromatic) 9.43 (br s, 1H, N*H*), 9.63 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.4$, 15.3, 21.1, 61.1, 120.3, 123.1, 128.6, 128.7, 130.8, 135.5, 138.2, 138.3, 160.9, 186.8; EI-MS *m/z* (%)=303 (M^+, 100), 257, 256 (33), 224 (27), 196 (31), 159 (15), 115 (9). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.18; H, 5.52; N, 4.73.

3.5.3. Ethyl 4-formyl-5-(methylsulfanyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (5c). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-1-(methylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate **4c** (2.80 g, 10 mmol) as colorless plates. Yield 2.54 g (88%), mp 119–120 °C. IR (KBr) $\nu_{max}=3247$, 1692, 1655, 1549, 1247, 1173, 1021, 795 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.55 (s, 3H, SCH_3), 4.11 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.32 (m, 5H, aromatic) 9.34 (br s, 1H, N*H*), 9.55 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=13.9$, 15.1, 60.8, 120.2, 123.0, 127.6, 128.0, 130.6, 131.5, 134.9, 137.7, 160.6, 186.2; EI-MS *m/z* (%)=289 (M^+, 90), 288 (84), 242 (76), 214 (33), 181 (100), 171 (23), 144 (71). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.12; H, 4.70; N, 4.95.

3.5.4. Ethyl 3-(4-bromophenyl)-5-(ethylsulfanyl)-4-formyl-1*H*-pyrrole-2-carboxylate (5d). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-bromophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4d** (3.70 g, 10 mmol) as colorless plates. Yield 3.4 g (89%), mp 148–149 °C. IR (KBr) $\nu_{max}=3254$, 1673, 1538, 1418, 1234, 1013, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 1.37 (t, 3H, $J=7$ Hz, SCH_2CH_3), 3.06 (q, 2H, $J=7$ Hz, SCH_2CH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.26 (d, 2H, $J=8$ Hz, aromatic), 7.53 (d, 2H, $J=8$ Hz, aromatic) 9.74 (br s, 1H, N*H*), 9.85 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.2$, 27.3, 51.7, 119.9, 123.8, 127.7, 128.0, 130.4, 131.3, 134.8, 135.9, 160.8, 186.3, 186.4; EI-MS *m/z* (%)=383 ($M^+ +2$, 100) 381 (M^+, 96), 350 (84), 348 (84), 302 (72), 304 (70), 276 (24), 274 (23), 225 (29), 223 (38), 199 (17), 144 (16). Anal. Calcd for $C_{16}H_{16}BrNO_3S$: C, 50.27; H, 4.22; N, 3.66. Found: C, 50.45; H, 4.11; N, 3.52.

3.5.5. Methyl 5-(ethylsulfanyl)-4-formyl-3-phenyl-1*H*-pyrrole-2-carboxylate (5e). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-1-(ethylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate **4e** (2.65 g, 10 mmol) as colorless plates. Yield 2.36 g (82%), mp 86–87 °C. IR (KBr) $\nu_{max}=3358$, 1682, 1651, 1539, 1386, 1233, 1154, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, $J=7$ Hz, SCH_2CH_3), 3.08 (q, 2H, $J=7$ Hz, SCH_2CH_3), 3.69 (s, 3H, OCH_3), 7.39 (m, 5H, aromatic), 9.69 (s, 1H, C*H*O), 9.72 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=$

14.8, 28.4, 61.4, 120.6, 122.6, 124.4, 130.9, 131.0, 132.5, 133.0, 136.3, 160.7, 186.4; EI-MS *m/z* (%)=289 (M^+, 78), 256 (76), 224 (100), 196 (39), 172 (16), 145 (60), 102 (11). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.08; H, 5.38; N, 4.71.

3.5.6. Methyl 4-formyl-3-(4-methylphenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (5f). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4f** (2.93 g, 10 mmol) as colorless plates. Yield 2.45 g (85%), mp 108–109 °C. IR (KBr) ν_{max}=3155, 1717, 1642, 1563, 1510, 1260, 1151, 1098, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J*=7 Hz, SCH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 3.09 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.72 (s, 3H, OCH_3), 7.21 (d, 2H, *J*=8 Hz, aromatic), 7.29 (d, 2H, *J*=8 Hz, aromatic) 9.71 (s, 1H, C*H*O), 9.79 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.6, 21.7, 27.7, 52.1, 120.2, 124.2, 128.6, 128.8, 130.7, 135.4, 136.3, 138.2, 161.2, 187.0; EI-MS *m/z* (%)=303 (M^+, 88), 270 (55), 238 (100), 210 (35), 186 (10), 159 (36), 128 (6), 115 (16). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.48; H, 5.54; N, 4.47.

3.5.7. Methyl 3-(4-chlorophenyl)-5-(ethylsulfanyl)-4-formyl-1*H*-pyrrole-2-carboxylate (5g). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4g** (3.1 g, 10 mmol) as colorless plates. Yield 2.8 g (88%), mp 128–129 °C. IR (KBr) ν_{max}=3124, 1696, 1649, 1439, 1242, 1084, 878, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J*=7 Hz, SCH_2CH_3), 3.07 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.71 (s 3H, OCH_3), 7.32 (d, 2H, *J*=8 Hz, aromatic), 7.36 (d, 2H, *J*=8 Hz, aromatic), 9.74 (s, 1H, C*H*O), 10.13 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.7, 28.2, 52.2, 120.7, 124.3, 128.4, 130.3, 132.1, 133.8, 134.5, 136.7, 161.0, 186.5; EI-MS *m/z* (%)=325 (M^++2, 37) 323 (M^+, 93), 290 (94), 258 (100), 230 (31), 207 (12), 179 (52), 144 (9), 113 (5). Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33. Found: C, 55.48; H, 5.50; N, 4.12.

3.5.8. Ethyl (5-ethylsulfanyl)-4-formyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (5h). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-1-(ethylsulfanyl)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]amino}acetate **4h** (3.2 g, 10 mmol) as colorless plates. Yield 2.9 g (88%), mp 92–93 °C. IR (KBr) ν_{max}=3247, 1661, 1509, 1247, 1176, 1034, 816, 781 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J*=7 Hz, SCH_2CH_3), 1.42 (t, 3H, *J*=7 Hz, OCH_2CH_3), 3.12 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.90 (s, 3H, $ArOCH_3$), 4.26 (q, 2H, *J*=7 Hz, OCH_2CH_3), 6.98 (d, 2H, *J*=8 Hz, aromatic), 7.38 (d, 2H, *J*=8 Hz, aromatic), 9.61 (br s, 1H, N*H*), 9.77 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.0, 14.3, 27.7, 55.2, 60.8, 113.1, 120.3, 123.7, 124.2, 131.8, 134.4, 135.4, 159.5, 160.5, 186.5; EI-MS *m/z* (%)=333 (M^+, 63), 300 (23), 254 (100), 226 (41), 174 (55), 158 (16), 132 (24). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.39; H, 5.92; N, 4.07.

3.5.9. Ethyl 3-(methylsufanyl)-4,5-dihydro-2*H*-benzo(*e*)-isoindole-1-carboxylate (13). Obtained by the Vilsmeier reaction of ethyl 2-({methylsulfanyl)[1-oxo-3,4-dihydro-2(1*H*)naphthalenyliden]amino}acetate **12** (3 g, 10 mmol) as colorless plates. Yield 2 g (78%), mp 131–133 °C. IR (KBr) ν_{max}=3271, 3057, 2986, 1660, 1412, 1209, 1020, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J*=7 Hz, OCH_2CH_3), 2.33 (s, 3H, SCH_3), 2.68 (t, 2H, *J*=6 Hz, CH_2CH_2), 2.85 (t, 2H, *J*=6 Hz, CH_2CH_2), 4.38 (q, 2H, *J*=7 Hz, OCH_2CH_3), 7.21 (m, 3H, aromatic), 8.40 (d, 1H, *J*=7 Hz, aromatic), 9.15 (br s, 1H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 20.1, 20.8, 31.1, 61.0, 118.7, 122.5, 126.8, 127.4, 127.6, 127.8, 128.4, 128.8, 130.9, 137.8, 160.8 ppm. EI-MS *m/z* (%)=287 (M^+, 94), 241 (56), 213 (43), 198 (72), 179 (100), 167 (32), 127 (35), 109 (18). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.72; H, 6.08; N, 4.72.

3.6. General procedure for the base catalyzed cyclization of β-oxoketene-*N*,*S*-acetals (14)

A solution of ketene-*N*,*S*-acetal **4** (10 mmol) in dry toluene (15 mL) was heated at 100–110 °C for 3 h. During this period DBU (20 mmol) was added in three equal portions to the reaction mixture. After the completion of the reaction (TLC), toluene was evaporated under reduced pressure and the residue was dissolved in dichloromethane, washed with 5% HCl (2×20 mL), then with saturated bicarbonate (2×20 mL) and finally with water (2×50 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a dark brown oil, which on column chromatography using hexane–ethyl acetate (9/1) as eluent afforded moderated yields of the 3-aryl pyrrole-2-carboxylates **14**.

3.6.1. Methyl 3-(4-chlorophenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (14a). Obtained by the cyclization of methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4a** (3.10 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1 g (34%), mp 138–139 °C. IR (KBr) ν_{max}=3297, 1673, 1447, 1262, 1002, 816, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J*=7 Hz, SCH_2CH_3), 2.81 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.78 (s, 3H, OCH_3), 6.39 (d, 1H, *J*=3 Hz, pyrrole C*H*), 7.33 (d, 2H, *J*=8 Hz, aromatic), 7.46 (d, 2H, *J*=8 Hz, aromatic), 9.26 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=15.6, 31.2, 51.8, 118.3, 119.7, 126.6, 128.3, 131.0, 133.4, 133.5, 161.0; EI-MS *m/z* (%)=297 (M^++2, 35) 295 (M^+, 91), 235 (92), 206 (56), 167 (78), 149 (67), 129 (100), 111 (42). Anal. Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.74. Found: C, 56.68; H, 4.88; N, 4.82.

3.6.2. Ethyl 5-(ethylsulfanyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (14b). Obtained by the cyclization of ethyl 2-{[(*E*)-3-phenyl-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4b** (2.90 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1.2 g (45%), mp 63–64 °C. IR (KBr) ν_{max}=3292, 1678, 1426, 1265, 1016, 822, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 6H, *J*=7 Hz, SCH_2CH_3+OCH_2CH_3), 2.80 (q, 2H, *J*=7 Hz, SCH_2CH_3), 4.26 (q, 2H, *J*=7 Hz, OCH_2CH_3), 6.42 (d, 1H, *J*=3 Hz, pyrrole C*H*), 7.31 (m, 3H, *J*=7.8 Hz, aromatic), 7.53 (d, 2H, *J*=7 Hz, aromatic), 9.38 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.1, 15.1, 30.8, 60.4, 118.2, 119.6, 125.6, 127.0, 127.6, 129.4, 132.9, 134.5, 160.5; EI-MS *m/z* (%)=275 (M^+, 92), 232 (84), 168 (52), 147 (54), 115 (19) and 105 (100). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.62; H, 6.08; N, 5.22.

3.6.3. Ethyl 3-(4-chlorophenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (14c). Obtained by the cyclization of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4c** (3.10 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 0.94 g (32%), mp 129–130 °C. IR (KBr) $\nu_{max}=3275$, 1672, 1493, 1259, 1087, 815, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.47 (s, 3H, SCH_3), 4.23 (q, 2H, $J=7$ Hz, OCH_2CH_3), 6.33 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.31 (d, 2H, $J=7$ Hz, aromatic), 7.46 (d, 2H, $J=7$ Hz, aromatic), 9.22 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 19.8, 60.91, 116.0, 119.6, 128.2, 128.6, 131.1, 132.2, 133.4, 160.6; EI-MS *m/z* (%)=297 ($M^+ +2$, 35) 295 (M^+, 91), 249 (72), 221 (100), 206 (33), 187 (26), 149 (48), 136 (38). Anal. Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.74. Found: C, 56.68; H, 4.88; N, 4.87.

3.6.4. Ethyl 3-(4-bromophenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (14d). Obtained by the cyclization of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4d** (3.70 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1 g (28%), mp 110–111 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 6H, $J=7$ Hz, $SCH_2CH_3+OCH_2CH_3$), 2.81 (q, 2H, $J=7$ Hz, SCH_2CH_3), 4.26 (q, 2H, $J=7$ Hz, OCH_2CH_3), 6.44 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.13 (d, 2H, $J=7$ Hz, aromatic), 7.20 (d, 2H, $J=7$ Hz, aromatic), 9.38 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 15.6, 31.3, 61.0, 118.3, 120.0, 121.6, 126.4, 131.1, 131.5, 132.1, 133.9 and 160.7; EI-MS *m/z* (%)=355 ($M^+ +2$, 31) 353 (M^+, 94), 294 (75), 249 (100), 230 (25), 181 (36), 157 (78). Anal. Calcd for $C_{15}H_{16}BrNO_2S$: C, 50.86; H, 4.55; N, 3.95. Found: C, 50.98; H, 4.68; N, 3.80.

3.6.5. Methyl 3-(4-methylphenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (14e). Obtained by the cyclization of methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4e** (2.80 g, 10 mmol) as colorless plates. Yield 0.62 g (24%), mp 120–121 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H, $ArCH_3$), 2.46, (s 3H, SCH_3), 3.77 (s, 3H, OCH_3), 6.34 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.17 (d, 2H, $J=8$ Hz, aromatic), 7.42 (d, 2H, $J=8$ Hz, aromatic), 9.09 (br s, 1H, N*H*) ppm. EI-MS *m/z* (%)=261 (M^+, 100), 229 (48), 201 (83), 186 (58), 168 (34), 115 (38) and 100 (16). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.18; H, 5.88; N, 5.52.

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18. ^{13}C NMR spectra of compound **3** showed signals of keto and enol tautomers. The values given are of the major tautomer.