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Graphical Abstract

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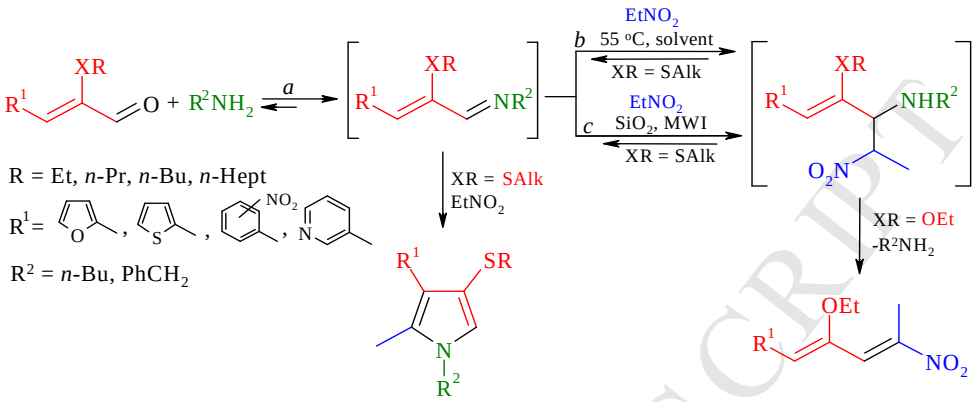

One-pot, three-component cascade synthesis of new tetrasubstituted pyrroles by coupling reaction of 2-functionally substituted 2-alkenals, amines and nitroethane

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Abstract

The reactivity of 2-alkylthio(2-alkoxy)-substituted 3-aryl(hetaryl)propenals in a one-pot three-component reaction with primary amines and nitroethane has been studied. A method for the synthesis of highly functionalized pyrroles (in 36-80% yields) from 2-alkylthiopropenals has been developed on the basis of this reaction. It is found that the reaction proceeds via formation of the intermediate imine of the starting enal, which undergoes 1,2-addition by nitroethane to give kinetically controlled 2-alkylthio-3-alkylamino-1-aryl(hetaryl)-4-nitro-pentene. When left to stand, upon heating or under microwave-assistance, this adduct can be transformed into the thermodynamically controlled 1,4-adduct. The latter undergoes intramolecular cyclization to afford the target pyrrole. A possibility of such isomerization of addition products of nitroalkane to 2-functionalized α,β-unsaturated imines is revealed for the first time. Scope of the reaction depending upon its conditions as well as structure of the starting substrates and amines has been studied.

Keywords: functionalized pyrroles, multicomponent protocol, substituted 2-enals (2-enimines) 1.2- vs 1.4-addition

1. Introduction

The pyrrole core is a ubiquitous structural unit of many natural compounds including hemoglobin, chlorophyll, vitamin B_{12}, L-tryptophan,[1] alkaloids,[2] as well as numerous essential drugs[3] and synthetic pharmacologically valuable substances possessing antibacterial,[4] antifungal,[5] antioxidant,[6] antitumor and anti-HIV activity.[2b,7] Each original substituent or new combination of substituents in the pyrrole cycle endows the compounds with new kind or even new spectrum of biological activity.[4-8] Tetrasubstituted pyrroles are of paramount importance owing to their antibacterial,[3a,9a-d] antiviral, antitumor[9e-h] and antioxidant[6a] activities and ability of inhibiting the cytokine-mediated diseases.[8d, 9i] In addition, pyrroles are employed as special pigments and dyes.[10]

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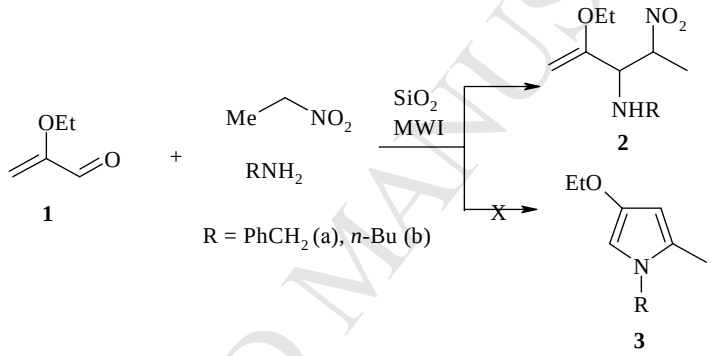
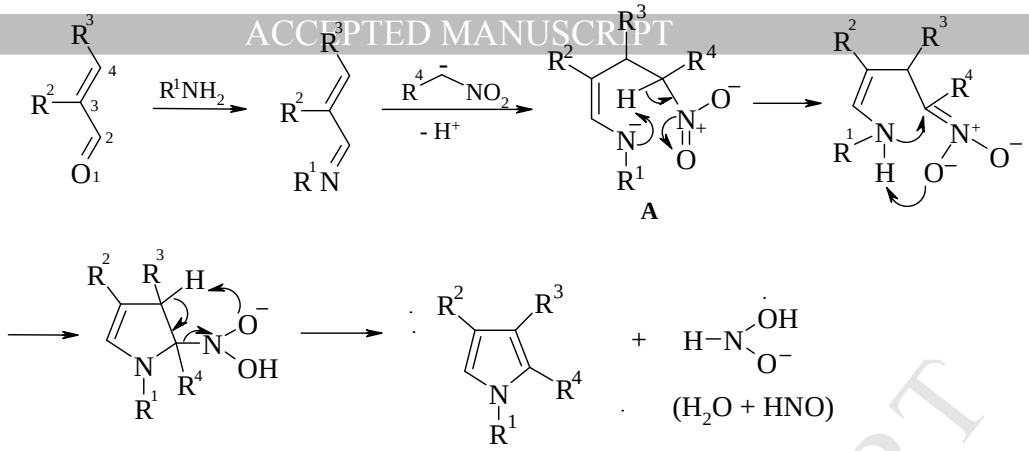
insecticides[11] and versatile building blocks in organic synthesis and materials chemistry.[12] Therefore, nowadays great effort is invested into the development of efficient methods for the synthesis of pyrroles[13] including tetrasubstituted ones.[9i,14] As a consequence, a lot of amazing progress has been achieved in the elaboration of elegant synthetic methodologies allowing structurally diverse pyrroles to be prepared.

Among numerous approaches to the synthesis of pyrroles, multicomponent coupling reactions arrest a special attention. Over the last decade, a great deal of publications has been devoted to these reactions.[13f,14c,14h,15] Quite rare, but very successfully α,β-unsaturated aldehydes are used in these transformations as the starting reagents.[16] It should be noted that before our works, to the best of our knowledge, 2-functionally substituted 2-alkenals have not been applied in the synthesis of pyrrole.[17] Unlike 2-alkylalkenals,[16,18] 2-ethoxypropenal reacts with primary aliphatic amines and nitroethane in the presence of silica gel under microwave assistance to furnish 2-ethoxy-4-nitropentenes **2a,b** in 85% yield (^{1}H NMR) or 20-28% after distillation, instead of the expected pyrroles **3**.[17]



Scheme 1

It is assumed[16a] that the first stage of the discussed three-component reaction involves condensation of amine with α,β-unsaturated aldehyde (Scheme 2) to give an imine bearing lower positive charge on the C_2 atom as compared with a charge on carbonyl atom of the starting aldehyde. Such redistribution of electron density in the conjugated imine system should promote the subsequent successful attack of nitroalkane carbanion at the C_4 atom of ambident electrophile (Michael reaction).[16a] Generation of the intermediate anion **A** is a key stage in the multistage cascade assembly of pyrroles. Further the intermediate adduct **A** cyclizes via the cascade of three reactions to deliver the target heterocycle (Scheme 2).



Scheme 2

The results obtained by us suggest that under the conditions of Scheme 1, the intermediate imine adds nitroethane across the imino group, but not in the 1,4-position. Earlier, to gain a more penetrating insight into the prospects of targeted application of 2-functionalized 2-alkenals, we have calculated the distribution of electron density in these molecules using density functional theory (DFT) at the B3LYP/6-311+G** and MO6/6-311+G** levels with natural bond orbital (NBO) analyses.[17] The calculations have shown that in 2-alkylthiosubstituted alkenals, unlike their alkoxy analogs, changes in the direction of the C=C bond polarization towards carbon α-atom are observed that should facilitate the attack of C-nucleophiles at the β-carbon atom (via the Michael reaction).

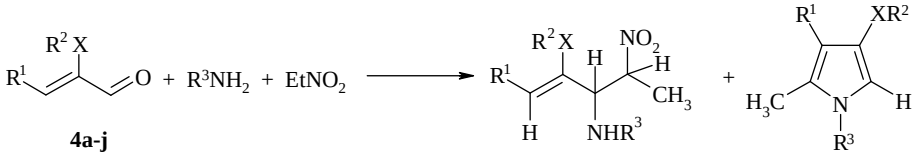
The present work deals with experimental verification of conditions used for the synthesis of tetrasubstituted pyrroles **5** via the three-component reaction between 2-functionalized 2-alkenals **4** of different electrophilicity and steric bulk, primary amines and nitroethane (Table 1). The scope of the reaction applicability have been experimentally studied to confirm the conclusions made previously by quantum-chemical calculation.[17]

2. Results and discussion

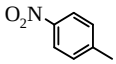
^{1}H NMR monitoring of the reaction has shown that like 2-alkoxypropenals[17] the three-component reaction of 2-butylthiopropenals **4a**,**b** both in THF at 50-60 ^{o}C (Table 1, entry 1) and with the reagents impregnated on an inorganic support (SiO_2) under MWI assistance (entries 2, 3) proceeds via quantitative formation of α,β-unsaturated imines **6** (reversible reaction *a* on Scheme 3) that allows such intermediates to be easily characterized using ^{1}H NMR technique. In solvents, at 50-60 ^{o}C this condensation is complete after a short period of time (< 0,5 h). Further (in 1-2 h), complete conversion of enimines **6** is observed and 1,2-adducts (**7**) are formed (the direction *b* on Scheme 3). In the ^{1}H NMR spectra, these compounds (usually mixtures of diastereoisomers) are readily detected by characteristic chemical shifts of C$\underline{H}_3$CH (two doublets in the region 1.40-1.55 ppm), NC*H (two signals at 3.95-4.10 ppm) and HC*NO_2 protons (two multiplets at 5.1-5.2 ppm). When the three-

component interaction is carried out under microwave assistance (direction *c* on Scheme 3), 1,2-adducts **7** are formed in five minutes and represent the major reaction products (70-75% in the mixture, ^{1}H NMR).

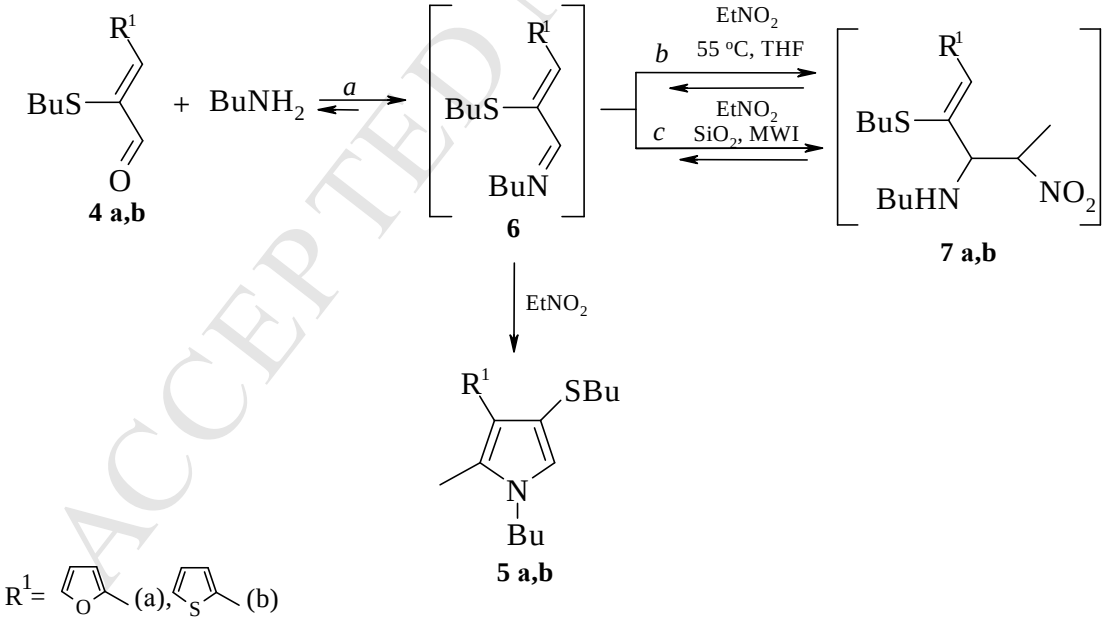
Table 1. Screening reaction conditions [a]



Entry	Starting 4	R^1	R^2X	R^3	MWI[b], SiO_2 / solvent	Time (h)	T °C	Product	Yield [c,d] (%)
1	4a		*n*-BuS	*n*-Bu	THF	4	60	**7a**	(98)[d]
2	4a		*n*-BuS	*n*-Bu	MWI	5 min	60	**7a**	(70)
3	4b		*n*-BuS	*n*-Bu	MWI	5 min	60	**7b**	(70)
4	4i	Ph	EtO	*n*-Bu	THF	7	55	**8b**[e]	45
5	4j		EtO	*n*-Bu	THF	9	55	**8c**[e]	36
6	4a		*n*-BuS	*n*-Bu	THF	9	55	**5a**	37
7	4c		*n*-PrS	*n*-Bu	MeOH	6	55	**5c**	53
8	4b		*n*-BuS	*n*-Bu	THF	18	55	**5b**	42
9	4b		*n*-BuS	$PhCH_2$	MeOH	10	55	**5d**	42
10	4d		$C_7H_{15}S$	*n*-Bu	MeOH	7.5	55	**5e**	56
11	4d		$C_7H_{15}S$	*n*-Bu	THF:MeOH 1:2.5	10	55	**5e**	74
12	4a		*n*-BuS	*n*-Bu	*i*-PrOH	6.5	80	**5a**	(72)[f]
13	4a		*n*-BuS	*n*-Bu	*i*-PrOH	8.5	55	**5a**	38 (64)[f]
14	4a		*n*-BuS	*n*-Bu	DMSO	1	150	**5a**	(70)[f]
15	4a		*n*-BuS	*n*-Bu	DMSO	12	55	**5a**	46 (90)[f]
16	4a		*n*-BuS	*n*-Bu	Solvent-free	12d	25	**7a : 5a**= 2 : 1	
17	4a		*n*-BuS	*n*-Bu	Solvent-free	4.5	55	**7a : 5a**= 1.7 : 1	
18	4a		*n*-BuS	*n*-Bu	Solvent-free	8	55	**5a**	(72)
19	4a		*n*-BuS	*n*-Bu	MeOH	8	55	**5a**	38
20	4a		*n*-BuS	$PhCH_2$	MeOH	14.5	55	**5f**	36

21	4e		*n*-BuS	$PhCH_2$	MeOH	13.5	55	**5g**	59
22	4f		*n*-PrS	*n*-Bu	MeOH	5	55	**5h**	80
23	4e		*n*-BuS	*n*-Bu	THF	15	55	**5i**	80
24	4g		*n*-BuS	*n*-Bu	MeOH	14	55	**5j**	60
25	4h		$C_7H_{15}S$	*n*-Bu	MeOH	14h	55	**5k**	67
26	4a		*n*-BuS	*n*-Bu	MWI	10 min	60	**7a : 5a=** 1 : 1	
27	4a		*n*-BuS	*n*-Bu	MWI	15 min	60	**5a**	(70)
28	4a		*n*-BuS	*n*-Bu	MWI	1 min	200	**5a**	(25)
29	4j		EtO	*n*-Bu	MWI	5 min	60	**8c**[e]	(98)

[a] Reaction condition: **4** : R^3NH_2 : $EtNO_2$ = 1 (1-4 mmol) : 1 : 3-4 (eq), solvent 1-3 ml.
[b] Microwave irradiation of reaction mixture on SiO_2.
[c] Isolated product after column chromatography.
[d] In parentheses yield determined by ^1H NMR analysis of the crude reaction mixture is given.
[e] The alternative direction of conversion of 2-alkoxy substituted adducts (**2c,d**) (Scheme 4)
[f] Yield of **7** or **5** were calculated by ^1H NMR integration of protons, using CH_2Br_2 as an internal standard.

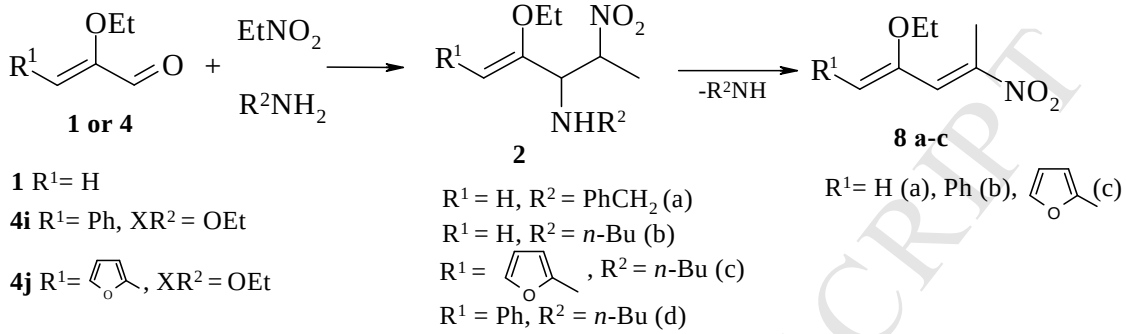


Scheme 3

An attempt to isolate adducts **7** by distillation in vacuum or column chromatography on SiO_2 results in their decomposition giving rise significant amounts of dibutyldisulfide (up to 50% in the reaction mixture) and tar.

Similar formation of 1,2-adducts **2c,d** (like previously synthesized 1,2-adducts **2a,b**[17]) is observed (Scheme 4) in the three-component reaction of 3-phenyl(or furyl)-substituted 2-

alkoxypropenals (**4i,j**) with amines and nitroethane (Table 1, entries 4,5). Compounds **2a-d** are unstable to vacuum distillation or column chromatography (SiO_2), and readily eliminate amine (Scheme 4) to furnish the corresponding nitropentadienes (**8**), isolated in low yields (28-36%) owing to their proneness to polymerization. Therefore the isolation of intermediates **2** as well as their thioanalogs **7** is beyond the scope of the present work, nevertheless their ^{1}H NMR spectra are given in the experimental part of the paper for all three-component reactions.



Scheme 4

We have unexpectedly found that upon long storage of the reaction mixtures (>10 days at 25 ^{o}C), the sulfur-containing 1,2-adducts (**7a,b**) are spontaneously and with complete conversion transformed into substituted pyrroles **5a,b** (Scheme 3), though a side-product, dibutyldisulfide, sometimes can be formed in noticeable amounts. Hence it follows that the synthesized 2-butylthiosubstituted aminonitropentenes **7a,b** are kinetically controlled reaction products. They can undergo the reverse reaction involving nitroethane elimination to deliver α,β-unsaturated imines **6**, which further are transformed into thermodynamically stable 1,4-isomers via 1,4-addition of nitroalkane. The latter, owing to the subsequent intramolecular cyclization of intermediate **A**, (Scheme 2) are converted to the stable pyrroles **5a,b**. Previously, such an effective conversion of 1,2-adduct of nitroalkane with α,β-enimine into 1,4-adduct has not been observed in experiments with 2-alkylalkenals under the conditions of three-component reaction of pyrrole synthesis.[16,18] Nevertheless, it is known that 1,4-adducts of C-nucleophiles to α,β-enals and enones are usually thermodynamically more stable than 1,2-adducts and therefore the latter can be transformed into 1,4-adducts, if the reaction of 1,2-addition is reversible.[19]

The reactivity of α,β-unsaturated enimines is similar to that of their carbonyl analogs. Like alkenals, they represent ambident electrophiles, which can participate in the reactions of 1,2- or 1,4-nucleophilic addition.[20] But unlike the oxygen analogs, the conjugated addition to α,β-unsaturated imines is not still clearly understood, probably due to the lower electrophilicity of these substrates.[21] Usually, such control of the regioselectivity is rather difficult and depends upon nucleophile and the reaction conditions, often 1,2-addition being preferable.[22]

Thus, we face a challenging task to define the experimental conditions favoring preferable formation of the thermodynamically controlled adducts. The issues of regioselective 1,2- or 1,4-

addition of C-nucleophiles to α,β-unsaturated aldehydes and ketones in the two-component reaction were[23] and still remain[24] the objects of careful research attention. According to the literature data, 1,4-addition is usually promoted by higher reaction temperature,[19c] more polar solvent (or mixture of solvents),[24в, 25] and the specific catalyst, appropriate for activation of both the reagent and substrate.[13f,26]

For better understanding of the reaction, we have studied the effect of solvent polarity on a rate of separate stages of the process (Table 1). The reaction completion is determined by evaluating the conversion of 1,2-adducts (**7**) using ^{1}H NMR technique. It should be noted that the reaction rate decreases with time. Therefore, to diminish the polymerization of 1,2-adduct and optimize the yield of pyrrole **5**, heating of the reaction mixture is sometimes stopped before reaching complete conversion. For the comparative analysis of the reaction parameters, the interaction of 2-alkylthio-3-furylpropenal **4a** with butyl amine and nitroethane (1 : 1 : 3-4 molar ratio, 1-4 mmol amounts, 55 ^{o}C) in the presence of a solvent (1-3 ml, proportional to the substrate amounts) has been chosen as a typical experiment. As a rule, the reactions are carried out without the additional catalyst. As is seen from Table 1, the reactions in THF, low-polar (ε 7.52) aprotic solvent ensuring low-solvating medium, proceed for 9-18 h (entries 6, 8 for structurally close substrates). In methanol (ε 32.6), the same reactions are carried out for 7-10 h (entries 7, 9-11).

Implementation of the reaction in 2-propanol (ε 18.3) allows the temperature of the reaction mixture to be increased up to 80 ^{o}C (entry 12). According to the ^{1}H NMR data (CH_2Br_2 as internal standard), in 2 h, complete conversion of unsaturated imine **6a** is observed; in 3.5 h, the yield of 1,2-adduct (**7a**) is 28%, and the yield of pyrrole **5a** reaches 33%. In 6.5 h, the target pyrrole becomes the major product of reaction mixture (72%). Unfortunately, the admixture of dibutyldisulfide in the mixture is 19%. When the reaction is carried out at 55 ^{o}C under nitrogen for the longer heating the needed for complete conversion of compound **7a** (8.5 h), the yield of the above admixture decreases to 4% (entry 13). However, after chromatographic isolation, the yield of pyrrole **5a** is 38%.

In DMSO (ε 46.68) at 150 ^{o}C, the reaction proceeds even faster (entry 14). Pyrrole **5a** is detected as a major product in the reaction mixture in 1 h, but the admixture of dibutyldisulfide attains 35%. When the reaction temperature decreases to 55 ^{o}C, quite deep conversion of 1,2-adducts (**7a**) occur for 12 h (entry 15). Meantime, the yield of the target product **5a** after isolation reaches 46%, and the yield of dibutyldisulfide is 35% (^{1}H NMR).

The rate of the standard reaction between aldehyde **4a**, butyl amine and nitroethane (1: 1: 3 molar ratio) can be raised considerably by performing the reaction under solvent-free conditions at room temperature (entry 16). In this case, nitroethane (ε 28.1) taken in excess amount, acts as a solvent. The ^{1}H NMR monitoring shows that in one day, imine **6a** is converted completely into 1,2 adduct. In 5 days **5a : 7a** ratio is 1 : 5, and in 12 days it becomes 2 : 1. Though the admixture of

dibutuldisulfide in this case is not high, this protocol can not be recommended because of slow dynamics of the reaction: total conversion of 1,2 adducts is reached only in 14 days.

To accelerate the process, the above described reaction has been carried out at 55 ^{o}C in the presence of 4.5-fold excess nitroethane (entry 17). Already in 1.5 h, the total disappearance of imine **6a** is observed and the reaction mixture contains two major products **7a** and **5a** in a 6 : 1 ratio, admixture of the disulfide being not high (8%). In 4.5 h, the ratio **7a : 5a** is equal 1.7 : 1. At a longer heating (8 h) in the absence of the solvent (entry 18), the ratio of products **7a** and **5a** becomes 1: 2.6 (the yield of **5a** is 72%, ^{1}H NMR). However, the total rate of the process under these conditions is comparable to rate of the reaction in methanol (*cf.* entries 18 and 19).

Further we have paid our attention to the amine component. It is found that aliphatic amines such as $BuNH_2$ and $PhCH_2NH_2$ (entries 9, 20, 21), readily tolerate the reaction, but the latter reacts significantly slower (*cf.* entries 21 and 22 or 19 and 20).

Since electrophilicity of enal is known[21в] to be of crucial importance in the formation of relative amounts of 1,2- and 1,4-adducts, a series of diverse 3-aryl (hetaryl)-2-alkylthio-2-propenals have been tested as the potential Michael acceptors.

To successfully implement the synthesis of pyrrole **5**, the initial substrate **4** should possess the ability of adding one nucleophile (RNH_2) in the 1,2-position, and the formed enamine **6** should add another nucleophile (nitroalkane anion) in the 1,4-position. Quantum-chemical calculation[17] and the experiments have shown that the functional substituents in the position 2 (OR and SR) have different effect on polarization of the carbonyl group and multiple bond. Owing to strong p-π-conjugation, the alkoxy moiety promotes a shift of electronic density toward the carbon β-atom. Formation of the intermediate imine proceeds easily, but in its molecule, the partial negative charge on β-atom only increases[17] thus hindering nitroethane attack at the β-atom. On the contrary, its attack across the imino group becomes preferable. For 2-alkylthio analogs, negative charge generated on β-atom is considerably less than in the case of alkoxy analog, and nitroethane can attack further the β-atom to afford a product of 1,4-addition (intermediate **A** in Scheme 2). This is the key intermediate product ensuring the successful synthesis of pyrrole **5**. Apparently, it is a highly reactive compound and its concentration in the mixture never reaches the values, which could be detected by ^{1}H NMR technique that has been done for the 1,4-addition reaction of 1,3-dicarbonyl C-anions to 2-butenal imine.[21в]

Diverse electron-donating and electron-withdrawing substituents in the 3 positionof the substrate can decrease or increase electronic density on the β-atom thus sometimes favoring the conjugate addition. In our research, among aromatic and heteroaromatic substituents in the 3 position, the pyridine cycle has been proved to exert the expressed electronic promotion to the formation of long conjugated system. In this case, the reactions proceed faster both in THF and MeOH, yields of the products reaching 60-80% (entries 21-23). Electronegative groups in *ortho*- or *para*-positions of the phenyl ring of compounds **4g,h** augment electrophilicity of the substrate and stimulate the conjugated

addition (entries 24, 25). When the substrates contain the furyl and thienyl moieties in the 3 position, yields of the target pyrroles **5a-d,f** are often lower (37-42%) (entries 6-8, 13, 20), though decrease of the yields can be due to duration of the heating.

The slowest stage of the studied reaction sequence is a retro 1,2-addition (see reversion reactions *b,c* on Scheme 3). Heating (entry 14) or microwave assistance are applied for successful implementation of this reaction. As is seen from Table 1 (entry 2), when the typical reaction is carried out on reagents-impregnated silica gel under microwave activation conditions, 1,2-adduct **7a** is formed at 60 ^{o}C for 5 min. Noteworthy, the rate of this reaction stage is 18-25 times higher than that of the reactions performed in a solvent at 55-60 ^{o}C. The reaction mixture is exposed in MWI reactor for 10 min at 60 ^{o}C to afford the target pyrrole **5a**, which is in equal ratio with adduct **7a**, a significant amount of dibutyldisulfide admixture (20 mol%) being also formed (entry 26). In 15 min, the ^{1}H NMR spectrum of the reaction mixture shows the increase of the admixture content up to 25 mol%, while the yield of the target product **5a** also rises to 70% (entry 27). An attempt to decrease the reaction time to 1 min at 200 ^{o}C results in the formation of pyrrole **5a** in 25% yield along with dibutyldisulfide in 74% yield (entry 28), while the intermediate 1,2-adducts (**7a**) is not observed at all. These experiments confirm that the high temperature and silica gel promote a decoupling RS-groups of the target products.

Unlike 2-alkylthiopropenal (**4a**), its oxygen analog, 2-ethoxy-3-(2-furyl)-propenal (**4j**), participates in microwave-initiated coupling reaction with nitroethane and butylamine for 5 min 60 ^{o}C (entry 29) to quantitatively furnish 2-ethoxy-1-(2-furyl)-4-nitropentadiene (**8c**).

3. Conclusions

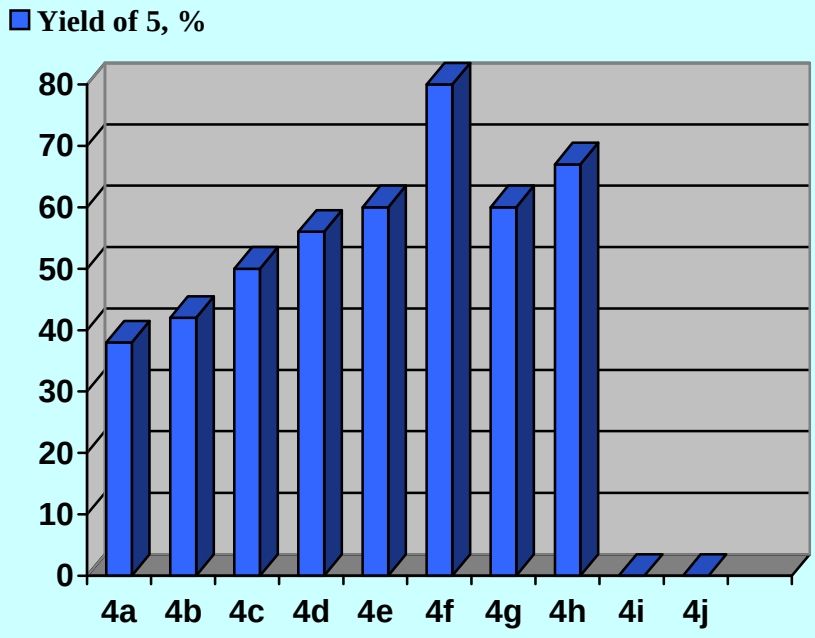


Fig. 1. Reactivity profile of 2-alkylthio(2-alkoxy)-substituted 3-aryl(hetaryl)propenals **4** depending on the structures of them in three-component cascade reaction with primary amines and nitroethane in synthesis pyrroles **5**.

- A method for the synthesis of densely functionalized pyrroles **5** with hitherto unknown combination of substituents has been developed. The method comprises the three-component cascade reaction of 3-aryl(hetaryl) 2-alkylthiosubstituted α,β-unsaturated aldehydes with primary amines and nitroethane (without additional promoters), the yields of the target products varying from moderated to high (Fig. 1).

- To the best of our knowledge, it has been found for the first time that the reactions involve the formation of kinetically controlled 1,2-adduct of nitroalkane to α,β-enimine, which can be transformed into the substituted pyrrole under the conditions developed (temperature 20-140 ^{o}C, solvents THF, MeOH, *i*-PrOH, DMSO or MWI promotor). Taking into account mechanistic aspects of the pyrrole synthesis,[16a] we believe that such transformation is triggered by isomerization of the kinetically controlled 1,2-adducts **7** into the thermodynamically controlled 1,4-adduct (**A**). The latter undergoes further intramolecular cyclization via the known sequence of domino reactions.

- The study of the protocol scope has revealed that, unlike 2-alkylthiopropenals, 2-alkoxy analogs regioselectively (up to 85% yield, ^{1}H NMR) give 1,2-adducts (**2**) of nitroethane to the intermediate imine, which are not capable of further isomerizing to pyrroles. Among the characteristic features of these adducts is an ability to readily eliminate the amine moiety upon distillation in vacuum, chromatographic isolation on silica gel or MWI activation thus transforming into 1-aryl(hetaryl)-2-alkoxy-4-nitro-pentadienes **8**, active monomers. Apparently, this feature is rationalized by the prevailing electron-donating effect of the alkoxy group inducing high partial negative charge on the carbon β-atom of the conjugated chain of both the substrate and an intermediate α,β-unsaturated imine.

4. Experimental section

4.1. General

^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on Bruker DPX 400 and AV-400 spectrometers (400.13, 100.61 and 40.56 MHz, accordingly), using $CDCl_3$ as a solvent, and HMDS as an internal standard. Nuclear Overhauser effect (NOESY), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) and inverse gradient heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HSQC and HMBC) were obtained using the standard Bruker pulse sequence for structural assignment of NMR spectra. GC-MS analysis was performed using Hewlett-Packard 5971A mass-selective detector (electron impact, 70 eV) coupled with an HP 5890 gas chromatograph (Ultra-2 column, 5% of phenylmethyl silicone; injector temperature 250 °C; oven temperature 70 to 280 °C; at rate of 20 °C min^{-1}). IR spectra were recorded as a thin film on a Bruker Vertex 70 spectrometer. Elemental analysis were carried out in a Thermo Finnigan automatic analyzer 1112 ser. Column chromatography was carried out over silica gel 60 (70-200 mesh; Merck). A microwave reactor Anton Paar "Monowave 300" was used.

The starting 2-functional substituted 2-alkenals were obtained by known methods.[27] Characterisation of 2-alkenals which were synthesized for the first time are given in section 4.4.

In ^{1}H NMR spectra of the intermediate products **7a-k** the doubling of all signals is present, which corresponds to the existence of diastereomers. Besides the additional doubling of proton signals of some groups (=CH, HC*NHR, HC*NO_2) is observed that provides evidence for the presence of two geometrical isomers.

4.2. Synthesis of 2-ethoxy-4-nitropentadienes 8a-c

*4.2.1. 2-Ethoxy-4-nitropentadiene (**8a**).* 3-Amino-2-ethoxy-4-nitropentene (**2a**) (1.7 g, 10.8 mmol) synthesized according to protocol[17] was chromatogrpaphed on silica gel (elution with hexane : ether 98 : 2) to give *2-ethoxy-4-nitropentadiene **8a*** as a clear dark-brown liquid, 0.47 g, 30% yield; [Found: C, 53.20; H, 6.87; N, 8.91. $C_7H_{11}NO_3$ requires C, 53.50; H, 7.01; N, 8.91%]; ν_{max} (film) cm^{-1}: 1727 (C=CNO_2), 1686 (C=C-OEt); δ_H (400 MHz, $CDCl_3$) 7.32 (1 H, s, CH=), 4.58 (2 H, s, CH_2=), 3.85 (2 H, q, *J* 7.0 Hz, CH_2 (Et)) 2.47 (3 H, s, CH_3), 1.37 (3 H, t, *J* 7.0 Hz, CH_3 (Et)); δ_C (100.6 MHz, $CDCl_3$) 159.7 (=C(OEt)), 151.9 (=C), 121.2 (CH=), 96.1 (CH_2=), 64.2 (OCH_2), 15.2 (CH_3), 13.4 (CH_3 (Et)); GC-MS: *m/z* (%) 157 (22, M^+), 111 (29), 83 (16), 65 (14), 53 (8), 43 (100).

*4.2.2. 2-Ethoxy-4-nitro-1-phenylpentadiene (**8b**).* A solution of (*Z*)-2-ethoxy-3-(2-phenyl)-propenal (**4i**) (0.25 g, 1.42 mmol), butylamine (0.1 g, 1.42 mmol) and nitroethane (0.32 g, 4.26 mmol) in THF (1.5 mL) was stirred at 55 ^{o}C for 7.5 h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (elution with $CHCl_3$) to give compound **8b** as a yellow oil 0.15 g, 45% yield; [Found: C, 66.6; H, 6.5; N, 6.1. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.4; N, 6.0%]; ν_{max} (film) cm^{-1}: 1727 (C=CNO_2), 1517, 1310, 1251, 1056; δ_H (400 MHz, $CDCl_3$) 7.69 (1 H, s, CH=CNO_2), 7.35 (2 H, t, *J* 7.8 Hz, *m*-H), 7.27 (1 H, t, *J* 7.8 Hz, *p*-H), 7.17 (2 H, d, *J* 7.8 Hz, *o*-H), 6.23 (1 H, s, =CH), 3.99 (2 H, q, *J* 6.9 Hz, OCH_2), 2.51 (3 H, s, CH_3), 1.45 (3 H, t, *J* 6.9 Hz, CH_3 (Et)); δ_C (100.6 MHz, $CDCl_3$) 149.7 (=C-O), 130.9 (C-NO_2), 129.6 (C_i), 129.4 (C_o), 128.7 (C_m), 127.4 (C_p), 125.8 (H<u>C</u>=CNO_2), 113.7 (=CH), 63.8 (OCH_2), 14.7 (CH_3), 14.6 (CH_3 (Et)); GC-MS: *m/z* (%) 233 (58, M^+), 186 (9), 157 (36), 129 (100), 115 (79), 91 (75), 77 (34), 29 (25, Et).

*4.2.3. 2-Ethoxy-1-furyl-4-nitropentadiene (**8c**).*

a) A solution of (*Z*)-2-ethoxy-3-(2-furyl)-propenal (**4j**) (0.4 g, 2.4 mmol) and butylamine (0.146 g, 2 mmol) in THF (2 mL) was stirred at 55 ^{o}C for 1 h, and then nitroethane (0.6 g, 8 mmol) was added and the mixture was stirred at the same temperature for 9 h. After evaporation of the solvent under reduced pressure, compound **8c** was isolated by column chromatography on silica gel (elution with $CHCl_3$) as an orange solid, mp 87 ^{o}C, 0.16 g, 36% yield; [Found: C, 59.43, H, 5.79; N, 6.25. $C_{11}H_{13}NO_4$ requires C, 59.18; H, 5.87; N, 6.28%.]; ν_{max} (KBr) cm^{-1}: 1715 (C=CNO_2), 1636, 1557, 1509, 1378, 1306; δ_H (400 MHz, $CDCl_3$) 8.25 (1 H, s, CH=CNO_2), 7.45 (1 H, d, *J* 1.8 Hz, H-5), 6.42 (1 H, dd, *J* 3.3, 1.8 Hz, H-4), 6.24 (1 H, d, *J* 3.3 Hz, H-3), 5.95 (1 H, s, =CH), 3.92 (2 H, q, *J* 7.0 Hz, OCH_2), 2.51 (3 H, s, CH_3), 1.43 (3 H, t, *J* 7.0 Hz, CH_3 (Et)); δ_C (100.6 MHz, $CDCl_3$) 150.2 (C-OEt), 146.2 (CNO_2), 143.0

(C-5), 129.6 (CH=CNO_2), 125.6 (C-2), 116.3 (CH=), 113.0 (C-3), 112.6 (C-4), 67.3 (OCH_2), 15.3 (Me in OEt), 13.6 (CH_3); GC-MS: *m/z* (%) 223 (100, M^+), 176 (16), 162 (14), 148 (39), 138 (30), 131 (10), 119 (44), 108 (52), 97 (79), 91 (76), 77 (52), 67 (51), 52 (56), 39 (36), 29 (38, Et). On storing the crystalline sample slowly is transformed into liquid geometrical isomer; δ_H (400 MHz, $CDCl_3$) 7.52 (1 H, s, CH=CNO_2), 7.42 (1 H, d, *J* 1.6 Hz, H-5), 6.86 (1 H, d, *J* 3.3 Hz, H-3), 6.48 (1 H, dd, *J* 3.3, 1.6 Hz, H-4), 6.28 (1 H, s, =CH), 3.86 (2 H, q, *J* 7.1 Hz, OCH_2), 2.50 (3 H, s, CH_3), 1.40 (3 H, t, *J* 7.1 Hz, CH_3 (Et)); δ_C (100.6 MHz, $CDCl_3$) 148.0 (C-OEt), 146.7 (CNO_2), 142.0 (C-5), 129.2 (CH=CNO_2), 124.6 (C-2), 111.9 (C-3), 108.4 (C-4), 102.9 (CH=), 64.0 (OCH_2), 14.7 (Me in OEt), 14.5 (CH_3).

b) Silica gel (1 g) was added to a solution of (*Z*)-2-ethoxy-3-(2-furyl)-propenal (**4j**) (0.08 g, 0.48 mmol), butylamine (0.035 g, 0.48 mmol), and nitroethane (0.11 g, 1.44 mmol) in dichloromethane (1 ml), and the reaction mixture was stirred at room temperature for 5-10 min. The solvent was completely removed and the reaction mixture was placed into a 10 ml vessel. After pressurization the reaction mixture was irradiated in single-mode microwave reactor at 60 ^oC for 5 min to give compound **8c** in 80% yield (NMR ^1H). ^1H NMR spectra correspond to that described above.

*3-Butylamino-2-ethoxy-1-(2-furyl)-4-nitro-2-pentene (**2c**).* δ_H (400 MHz, $CDCl_3$) 7.33 (1 H, d, *J* 1.6 Hz, H-5), 6.86 (1 H, d, *J* 3.5 Hz, H-3), 6.57 (1 H, dd, *J* 3.5, 1.6 Hz, H-4), 6.28 and 6.27 (major), 6.26 and 6.25 (minor) (1 H, s, =CH), 5.11 (major) and 5.06 (minor) (1 H, m, HC*NO_2), 4.78 (major) and 4.72 (minor) (1 H, m, NH), 4.06 and 4.04 (minor), 4.02 and 4.00 (major) (1 H, s, HC*NHBu), 3.82 (2 H, m, OCH_2), 3.52 (2 H, m, NCH_2), 1.43 (3 H, d, *J* 6.3 Hz, CH_3), 1.38-1.19 (7 H, m, $(CH_2)_2$ in NBu, CH_3 in OEt), 0.89 (3 H, t, *J* 7.2 Hz, CH_3 (NBu)).

4.3. General synthesis of pyrroles 5a-k

Method A:

A solution of butylamine (1 mmol) and α,β-unsaturated aldehydes (1 mmol) in solvent (1 mL) was stirred at 55 °C for 30 min, and then nitroethane (3-4 mmol) was added to the solution and the mixture was stirred at that temperature for 5-18 h. After removal of the solvent under reduced pressure, products were isolated by column chromatography (silica gel, eluent CH_2Cl_2 or $CHCl_3$).

Method B:

A solution of butylamine (1 mmol) and α,β-unsaturated aldehydes (1 mmol) and nitroethane (3-4 mmol) in solvent (1 mL) was stirred at 55-150 °C for 1-18 h. After removal of the solvent under reduced pressure, products were isolated by column chromatography (silica gel, eluent CH_2Cl_2 or $CHCl_3$).

Method C:

Silica gel (2 g) was added to a solution of butylamine (1 mmol), α,β-unsaturated aldehydes (1 mmol) and nitroethane (3-4 mmol) in dichloromethane, and the reaction mixture was stirred at room temperature for 5-10 min. The solvent was completely removed and the reaction mixture was placed

into a 10 ml vessel. After pressurization the reaction mixture was irradiated in single-mode microwave reactor at 60 ^{o}C for 1-15 min.

4.3.1. 1-Butyl-4-butylthio-3-(2-furyl)-2-methyl pyrrole (5a)

a) *Method B:* (*Z*)-2-butylthio-3-(2-furyl)propenal (0.15 g, 0.71 mmol), butylamine (0.052 g, 0.71 mmol) and nitroethane (0.16 g, 2.14 mmol) in *i*-PrOH (0.7 mL). The solution was stirred at 55 °C for 8.5 h. Yield of **5a** 64% (^{1}H NMR); isolated yield of **5a** 38% (0.078 g); ^{1}H, ^{13}C NMR spectra of compound **5a** correspond to those previously reported.[17] (Entry 13).

b) *Method B:* (*Z*)-2-butylthio-3-(2-furyl)propenal (0.23 g, 1.09 mmol), butylamine (0.08 g, 1.09 mmol) and nitroethane (0.246 g, 3.3 mmol) in MeOH (1 mL). The solution was stirred at 55 °C for 8 h. Isolated yield of **5a** 38% (0.12 g) (Entry 19).

c) *Method B:* (*Z*)-2-butylthio-3-(2-furyl)propenal (0.236 g, 1.12 mmol), butylamine (0.082 g, 1.12 mmol) and nitroethane (0.25 g, 3.37 mmol) in DMSO (1 mL). The solution was stirred at 150 °C for 1 h. Yield of **5a** 70% (^{1}H NMR) (Entry 14).

d) *Method C:* (*Z*)-2-butylthio-3-(2-furyl)propenal (0.127 g, 0.6 mmol), butylamine (0.044 g, 0.6 mmol) and nitroethane (0.136 g, 1.8 mmol). The vessel was irradiated by microwave at 60 °C for 15 min. Yield of **5a** 70% (^{1}H NMR) (Entry 27).

*3-Butylamino-2-butylthio-1-(2-furyl)-4-nitro-2-pentene (**7a**)* was obtained by method C (MWI for 5 min) from (*Z*)-2-butylthio-3-(2-furyl)propenal (0.317 g, 1.5 mmol), butylamine (0.11 g, 1.5 mmol) and nitroethane (0.34 g, 4.5 mmol). 1,2-Adduct **7a** is a mixture of diastereomers in 1.5:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.32 (major) and 7.25 (minor) (1 H, d, *J* 1.8 Hz, H-5'), 6.51 and 6.48 (major), 6.37 and 6.34 (minor) (1 H, s, CH=), 6.30 (minor) and 6.24 (major) (1 H, dd, *J* 3.2, 1.8 Hz, H-4'), 6.16 (major) and 6.14 (minor) (1 H, d, *J* 3.2 Hz, H-3'), 5.18 (minor) and 5.10 (major) (1 H, m, HC*NO_2), 4.60 (major) and 4.53 (minor) (1 H, m, NH), 3.96 and 3.93 (1 H, s, HC*NHBu), 3.07 (major) and 3.0 (minor) (2 H, m, NCH_2), 2.12 and 2.05 (2 H, m, SCH_2), 1.53 (minor) and 1.43 (major) (3 H, d, *J* 6.6 Hz, CH_3), 1.38-1.21 (8 H, m, $(CH_2)_2$ in SBu and NBu), 0.92 (3 H, t, *J* 7.3 Hz, CH_3 (SBu)), 0.82 (3 H, t, *J* 7.2 Hz, CH_3 (NBu)).

4.3.2. 1-Butyl-4-butylthio2-methyl-3-(2-thienyl)-pyrrole (5b) was obtained by method A.[17] ^{1}H and ^{13}C NMR spectra correspond to those previously reported.[17]

*3-Butylamino-2-butylthio-4-nitro-1-(2-thienyl)pentene (**7b**)* was obtained analogously to **7a** by method C (MWI for 5 min) from (*Z*)-2-butylthio-3-(2-thienyl)propenal (0.2 g, 0.884 mmol), butylamine (0.06 g, 0.884 mmol) and nitroethane (0.2 g, 2.65 mmol). 1,2-Adduct **7b** is a mixture of diastereomers in 1.5:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.16 (major) and 7.12 (minor) (1 H, d, *J* 4.7 Hz, H-5'), 6.94 (major) and 6.92 (minor) (1 H, d, *J* 3.6 Hz, H-3'), 6.90 (major) and 6.83 (minor) (1 H, dd, *J* 4.7 Hz, *J* 3.6 Hz, H-4'), 6.49 and 6.46 (minor), 6.38 and 6.35 (major) (1 H, s, CH=), 5.13 (1 H, m, HC*NO_2), 4.53 (minor) and 4.48 (major) (1 H, m, NH), 4.11 and 4.09 (major), 4.10 and 4.07 (minor) (1 H, s, HC*NHBu), 3.07 (minor) and 3.0 (major) (2 H, m, NCH_2), 2.10 (2 H, m, SCH_2), 1.52 (minor) and 1.41

(major) (3 H, d, *J* 6.6 Hz, CH_3),1.39-1.25 (8 H, m, $(CH_2)_2$ in SBu and NBu), 0.92 (3 H, t, *J* 7.4 Hz, CH_3 (SBu)), 0.82 (3 H, t, *J* 7.2 Hz, CH_3 (NBu)).

4.3.3. 1-Butyl-3-(2-furyl)-2-methyl-4-propylthio-pyrrole (5c) was obtained by *method A* from 3-furyl-2-propylthiopropenal (**4c**) (0.217 g, 1.1 mmol), butylamine (0.08 g, 1.1 mmol) and nitroethane (0.25 g, 3.3 mmol) in MeOH (1 mL). The solution was stirred at 55 °C for 6 h. Compound **5c** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil 0.16 g, 53% yield; [Found: C, 69.3; H, 8.1; N, 5.3; S, 11.4%. $C_{16}H_{23}OSN$ requires C, 69.3; H, 8.4; N, 5.05; S, 11.6%]; ν_{max}(film) 3334, 3115, 2960, 2872, 1551, 1456, 1417, 1378, 1360, 1336, 1292, 1235, 1145, 1010, 730 $см^{-1}$; δ_H (400 MHz, $CDCl_3$) 7.42 (1 H, dd, *J* 1.8, 0.8 Hz, H-5'), 6.67 (1 H, s, H-5), 6.64 (1 H, dd, *J* 3.3, 0.8 Hz, H-3'), 6.45 (1 H, dd, *J* 3.3, 1.8 Hz, H-4'), 3.78 (2 H, t, *J* 7.2 Hz, NCH_2), 2.53 (2 H, t, *J* 7.2 Hz, SCH_2), 2.37 (3 H, s, Me), 1.67 (2 H, m, $NCH_2\underline{CH_2}$), 1.55 (2 H, m, $NCH_2CH_2\underline{CH_2}$), 1.34 (2 H, m, $SCH_2\underline{CH_2}$), 0.97 (3 H, t, *J* 7.2 Hz, CH_3 (SPr)), 0.93 (3 H, t, *J* 7.2 Hz, CH_3 (NBu)); δ_C (100.6 MHz, $CDCl_3$) 151.6 (C-2'), 140.1 (C-5'), 127.7 (C-3), 125.4 (C-2), 125.2 (C-5), 114.5 (C-4), 110.8 (C-3'), 105.6 (C-4'), 46.7 ($N\underline{C}H_2$), 38.5 ($S\underline{C}H_2$), 33.1 ($NCH_2\underline{C}H_2$), 22.6 ($SCH_2\underline{C}H_2$), 19.9 ($NCH_2CH_2\underline{C}H_2$), 13.7 ($CH_3$ (NBu)), 13.3 (CH_3 (SPr)), 11.2 ($\underline{C}H_3$-C-2); δ_N (40.56 MHz, $CDCl_3$) -215.4; GC-MS: *m/z* (%) 277 (100, M^+), 249 (3, M-$(CH_2)_2$), 235 (61, M-$(CH_2)_3$), 192 (36), 160 (18), 29 (4).

*Butylimine of (Z)-3-(2-furyl)-2-propylthiopropenal (**6c**), intermediate in the synthesis of pyrrole **5c**.* δ_H (400 MHz, $CDCl_3$) 7.90 (1 H, s, HC=N), 7.45 (1 H, d, *J* 1.8 Hz, H-5'), 7.32 (1 H, dd, *J* 3.5 Hz, H-3'), 7.04 (1 H, s, CH), 6.51 (1 H, dd, *J* 3.5, 1.8 Hz, H-4'), 3.54 (2 H, t, *J* 7.3 Hz, NCH_2), 2.90 (2 H, t, *J* 7.3 Hz, SCH_2), 1.63 (2 H, m, $NCH_2C\underline{H_2}$), 1.55 (2 H, m, $NCH_2CH_2C\underline{H_2}$), 1.33 (2 H, m, $SCH_2C\underline{H_2}$), 0.94 (3 H, t, *J* 7.2 Hz, CH_3 (SPr)), 0.91 (3 H, t, *J* 7.2 Hz, CH_3 (NBu)).

*3-Butylamino-1-(2-furyl)-4-nitro-2-propylthiopentene (**7c**), intermediate in the synthesis of pyrrole* **5c**. 1,2-Adduct **7c** is a mixture of diastereomers in 1:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.32 and 7.25 (1 H, d, *J* 2.6 Hz, H-5'), 6.51 and 6.48, 6.38 and 6.35 (1 H, s, CH=), 6.31 and 6.25 (1 H, dd, *J* 3.0, 2.6 Hz, H-4'), 6.16 and 6.13 (1 H, d, *J* 3.0 Hz, H-3'), 5.21 and 5.11 (1 H, m, HC^*NO_2), 4.60 and 4.51 (1 H, m, NH), 3.97 and 3.95 (1 H, s, $\underline{H}C^*NHBu$), 3.05 and 3.00 (2 H, m, NCH_2), 2.12 and 2.02 (2 H, m, SCH_2), 1.53 and 1.43 (3 H, d, *J* 6.6 Hz, CH_3), 1.38 (6 H, m, $(CH_2)_2$ in SPr and NBu), 0.92 (3 H, t, *J* 7.7 Hz, CH_3 (SPr)), 0.82 (3 H, t, *J* 7.6 Hz, CH_3 (NBu)).

4.3.4. 1-Benzyl-4-butylthio-2-methyl-3-(2-thienyl)pyrrole (5d) was obtained analogously to **5c** by *method A* from (*Z*)-2-butylthio-3-(2-thienyl)propenal (**4b**) (0.4 g, 1.76 mmol), benzylamine (0.19 g, 1.76 mmol) and nitroethane (0.39 g, 5.3 mmol) in MeOH (3 mL). The solution was stirred at 55 °C for 10 h. Compound **5d** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.25 g, 42% yield; [Found C, 70.5; H, 6.7; N, 4.3; S, 18.4. $C_{20}H_{23}NS_2$ requires C, 70.4; H, 6.7; N, 4.1; S, 18.8%]; ν_{max}(film) 3066, 2958, 2872, 1606, 1552, 1497, 1454, 1354, 1222, 909, 734 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34-7.24 (4 H, m, *m*-H, *p*-H, H-5'), 7.04 (4 H, m, *o*-H, H-3', H-4'), 6.75 (1 H, s, H-5), 5.02 (2 H, s, $NC\underline{H_2}$), 2.47 (2 H, t, *J* 7.2 Hz, $SC\underline{H_2}$), 2.20 (3 H, s, Me), 1.42 (2 H, m, $SCH_2C\underline{H_2}$),

1.30 (2 H, m, $SCH_2CH_2C\underline{H}_2$), 0.81 (3 H, t, *J* 7.3 Hz, CH_3 (SBu)); δ_C (100.6 MHz, $CDCl_3$) 138 (C-2), 137.6 (C_i), 130.5 (C-2'), 128.5 (C_o), 128.3 (C_p), 127.3 (C-4'), 127.1 (C_m), 126.3 (C-3'), 126.1 (C-5), 124.7 (C-5'), 118.6 (C-3), 112.0 (C-4), 51.5 ($N\underline{C}H_2$), 36.9 ($S\underline{C}H_2$), 32.0 ($\underline{C}H_2Et$), 22.3 ($\underline{C}H_2CH_3$), 14.3 (CH_3 (Bu)), 11.6 ($\underline{C}H_3$-C-2); GC-MS: *m/z* (%) 341 (83, M^+), 285 (52, M-$(CH_2)_4$), 252 (22, M-SBu), 194 (24), 91 (100, CH_2Ph), 77 (13).

*Benzylimine of (Z)-2-butylthio-3-(2-thienyl)propenal (**6d**)*. δ_H (400 MHz, $CDCl_3$) 8.08 (1 H, s, CH=N), 7.50 (1 H, s, CH), 7.47 (1 H, d, *J* 5.0, H-5'), 7.20-7.37 (5 H, m, *o*-H, *m*-H, *p*-H), 7.06 (2 H, m, H-3', H-4'), 4.76 (2 H, s, $N\underline{C}H_2$), 2.84 (2 H, t, *J* 7.3 Hz, SCH_2), 1.51 (2 H, m, $SCH_2C\underline{H}_2$), 1.17 (2 H, m, $SCH_2CH_2C\underline{H}_2$), 0.80 (3 H, t, *J* 7.1 Hz, CH_3 (SBu)).

*3-Benzylamino-2-butylthio-4-nitro-1-(2-thienyl)pentene (**7d**), intermediate in the synthesis of pyrrole* **5d**. 1,2-Adduct **7d** is a mixture of diastereomers in 1.5:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.31 (6 H, m, *o*-H, *m*-H, *p*-H, H-5'), 7.13 (major) and 7.08 (minor) (1 H, dd, *J* 5.0, 3.5 Hz, H-4'), 6.94 (major) and 6.86 (minor) (1 H, dd, *J* 3.5, 1.6 Hz, H-3'), 6.59 and 6.56 (minor), 6.50 and 6.47 (major) (1 H, s, CH=), 5.16 (1 H, m, HC^*NO_2), 4.98 (major) and 4.87 (minor) (1 H, m, NH), 4.27 and 4.25 (major), 4.14 and 4.11 (minor) (1 H, s, $\underline{H}C^*NH$), 4.20 (2 H, m, NCH_2), 2.11 (2 H, m, SCH_2), 1.49 (minor) and 1.41 (major) (3 H, d, *J* 6.6 Hz, CH_3), 1.25 (4 H, m, $(CH_2)_2$ in SBu), 0.90 (3 H, t, *J* 7.5 Hz, CH_3 (SBu)).

4.3.5. 1-Butyl-3-(2-furyl)-4-heptylthio-2-methyl pyrrole (5e) was obtained by *method A* from (*Z*)-3-(2-furyl)-2-heptylthiopropenal (**4d**) (0.45 g, 1.8 mmol), butylamine (0.13 g, 1.8 mmol) and nitroethane (0.4 g, 5.3 mmol) in MeOH (3 mL). The solution was stirred at 55 °C for 7.5 h. Compound **5e** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.34 g, 56% yield; [Found: C, 72.0; H, 9.15; N, 4.1; S, 9.6. $C_{20}H_{31}OSN$ requires C, 72.2; H, 9.1; N, 4.2; S, 9.6%]; ν_{max}(film) 3384, 3116, 2956, 2926, 2855, 1552, 1458, 1417, 1361, 1336, 1300, 1148, 1011, 724 $см^{-1}$; δ_H (400 MHz, $CDCl_3$) 7.40 (1 H, d, *J* 2.0 Hz, H-5'), 6.63 (1 H, s, H-5), 6.61 (1 H, d, *J* 3.2 Hz, H-3'), 6.41 (1 H, dd, *J* 3.2, 2.0 Hz, H-4'), 3.77 (2 H, t, *J* 7.2 Hz, $N\underline{C}H_2$), 2.52 (2 H, t, *J* 7.2 Hz, SCH_2), 2.36 (3 H, s, Me), 1.33-1.12 (14 H, m, $(C\underline{H}_2)_7$ (SHept, NBu)), 0.88 (3 H, t, *J* 7.2 Hz, CH_3 (SHept)), 0.86 (3 H, t, *J* 7.5 Hz, CH_3 (NBu)); δ_C (100.6 MHz, $CDCl_3$) 143.2 (C-2'), 140.0 (C-5'), 127.5 (C-2), 125.1 (C-5), 114.5 (C-3), 110.8 (C-4), 109.4 (C-3'), 105.8 (C-4'), 46.6 ($N\underline{C}H_2$), 36.4 ($S\underline{C}H_2$), 33.1 ($NCH_2\underline{C}H_2$), 31.5 ($SCH_2\underline{C}H_2$), 30.3 ($NCH_2CH_2\underline{C}H_2$), 29.0 (4C, $SCH_2CH_2(\underline{C}H_2)_2$), 13.7 (2C, CH_3 (SHept, NBu)), 11.2 ($\underline{C}H_3$-C-2); GC-MS: m/z (%) 333 (100, M^+), 235 (90, M-$(CH_2)_7$), 202 (17, M-SHept), 192 (20), 29 (5).

*Butylimine of (Z)-3-(2-furyl)-2-heptylthiopropenal (**6e**)*. δ_H (400 MHz, $CDCl_3$) 7.90 (1 H, s, CH=N), 7.47 (1 H, d, *J* 1.8 Hz, H-5'), 7.31 (1 H, d, *J* 3.5 Hz, H-3'), 7.04 (1 H, s, =CH), 6.50 (1 H, dd, *J* 3.5, 1.8 Hz, H-4'), 3.55 (2 H, t, *J* 7.0 Hz, $N\underline{C}H_2$), 2.90 (2 H, t, *J* 7.4 Hz, SCH_2), 1.62 (2 H, m, $NCH_2C\underline{H}_2$), 1.51 (2 H, m, $SCH_2C\underline{H}_2$), 1.37-1.25 (10 H, m, $(C\underline{H}_2)_5Me$ (SHept, NBu)), 0.87 (3 H, t, *J* 7.1 Hz, CH_3 (NBu)), 0.84 (3 H, t, *J* 7.2 Hz, CH_3 (SHept)).

*3-Butylamino-1-(2-furyl)-2-hepylthio-4-nitropentene (**7e**).* 1,2-Adduct **7e** is a mixture of diastereomers in 1.5:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.32 (major) and 7.25 (minor) (1 H, d, *J* 1.8 Hz, H-5'), 6.52 and 6.49 (minor), 6.38 and 6.35 (major) (1 H, s, CH=), 6.30 (minor) and 6.24 (major) (1 H, dd, *J* 3.2, 1.8 Hz, H-4'), 6.16 (major) and 6.14 (minor) (1 H, d, *J* 3.2 Hz, H-3'), 5.19 (minor) and 5.10 (major) (1 H, m, HC^*NO_2), 4.61 (major) and 4.54 (minor) (1 H, m, NH), 3.96 and 3.94 (1 H, s, $\underline{H}C^*NH$), 3.07 (major) and 3.0 (minor) (2 H, m, NCH_2), 2.12 and 2.00 (2 H, m, SCH_2), 1.50 (minor) and 1.44 (major) (3 H, d, *J* 6.6 Hz, CH_3), 1.38-1.11 (14 H, m, $(CH_2)_7$ in SHept and NBu), 0.93 (3 H, t, *J* 7.7 Hz, CH_3 (SHept)), 0.83 (3 H, t, *J* 7.6 Hz, CH_3 (NBu)).

4.3.6. 1-Benzyl-4-butylthio-3-(2-furyl)-2-methyl pyrrole (5f) was obtained analogously to ***5e*** by *method A* from (*Z*)-2-butylthio-3-(2-furyl)propenal (**4a**) (1 g, 4.76 mmol), benzylamine (0.42 g, 4 mmol) and nitroethane (0.89 g, 12 mmol) in MeOH (5 mL). The solution was stirred at 55 °C for 14.5 h. Compound **5f** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.46 g, 36% yield; [Found: C, 73.6; H, 6.9; N, 4.5; S, 10.1. $C_{20}H_{23}OSN$ requires C, 73.8; H, 7.1; N, 4.3; S, 9.85%]; ν_{max}(film) 3114, 2957, 2872, 1607, 1554, 1497, 1454, 1416, 1385, 1355, 1332, 1300, 1145, 1010, 730 $см^{-1}$; δ_H (400 MHz, $CDCl_3$) 7.40 (1 H, d, *J* 1.9 Hz, H-5'), 7.25 (3 H, m, *m*-H, *p*-H), 7.01 (2 H, d, *J* 7.3 Hz, *o*-H), 6.71 (1 H, s, H-5), 6.67 (1 H, d, *J* 3.2 Hz, H-3'), 6.43 (1 H, dd, *J* 3.2, 1.9 Hz, H-4'), 5.01 (2 H, s, $NC\underline{H}_2$), 2.57 (2 H, t, *J* 7.2 Hz, $SC\underline{H}_2$), 2.30 (3 H, s, Me), 1.50-1.26 (4 H, 2 m, $C\underline{H}_2$Me (SBu)), 0.83 (3 H, t, *J* 7.4 Hz, CH_3 (SBu)); δ_C (100.6 MHz, $CDCl_3$) 150.8 (C-2'), 140.2 (C-5'), 137.5 (C_i), 129.0(C_o), 128.2 (C-2), 127.2 (C_p), 126.5 (C_m), 125.1 (C-5), 115.0 (C-3), 110.5 (C-3'), 110.2 (C-4), 106.1 (C-4'), 50.7 ($N\underline{C}H_2$), 36.0 ($S\underline{C}H_2$), 31.5 ($\underline{C}H_2$Et), 21.9 ($\underline{C}H_2CH_3$), 13.8 (CH_3 (Bu)), 11.4 ($\underline{C}H_3$-C-2); GC-MS: *m/z* (%) 325 (100, M^+), 269 (57, M-$(CH_2)_4$), 236 (20, M-SBu), 178 (24), 91 (94, CH_2Ph).

*Benzylimine of (Z)-2-butylthio-3-(2-furyl)propenal (**6f**).* δ_H (400 MHz, $CDCl_3$) 8.02 (1 H, s, CH=N), 7.47 (1 H, d, *J* 1.6, H-5'), 7.37-7.28 (5H, m, *o*-H, *m*-H, *p*-H), 7.09 (1 H, s, HC=), 6.51 (1 H, dd, *J* 3.2, 1.6 Hz, H-4'), 6.30 (1 H, d, *J* 3.2 Hz, H-3'), 4.76 (2 H, s, $NC\underline{H}_2$), 2.78 (2 H, t, *J* 7.4 Hz, $SC\underline{H}_2$), 1.30-1.18 (4 H, m, $SCH_2C\underline{H}_2C\underline{H}_2$), 0.80 (3 H, t, *J* 7.4 Hz, CH_3 (SBu)).

*3-Benzylamino-2-butylthio-4-nitro-1-(2-furyl)pentene (**7f**).* 1,2-Adduct **7f** is a mixture of diastereomers in 1:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.38-7.21 (6 H, m, *o*-H, *m*-H, *p*-H, H-5'), 6.59 and 6.56, 6.49 and 6.46 (1 H, s, HC=), 6.31 and 6.25 (1 H, dd, *J* 3.2, 1.5 Hz, H-4'), 6.20 and 6.16 (1 H, d, *J* 3.2 Hz, H-3'), 5.22 and 5.10 (1 H, m, HC^*NO_2), 4.97 and 4.88 (1 H, m, NH), 4.26 and 4.25, 4.20 and 4.19 (1 H, s, $\underline{H}C^*NH$), 3.99 (2 H, m, NCH_2), 2.13 and 2.05 (2 H, m, SCH_2), 1.46 and 1.43 (3 H, d, *J* 6.6 Hz, CH$\underline{\text{Me}}$), 1.40-1.18 (4 H, m, $SCH_2C\underline{H}_2C\underline{H}_2$), 0.80 (3 H, t, *J* 7.4 Hz, CH_3 (SBu)).

4.3.7. 1-Benzyl-4-butylthio-2-methyl-3-(3-pyridyl)pyrrole (5g) was obtained analogously to **5f** by *method A* from benzylamine (0.145 g, 1.4mmol), (*Z*)-2-butylthio-3-(3-pyridyl)propenal (**4e**) (0.3 g, 1.4 mmol) and nitroethane (0.59 g, 7.9 mmol) in MeOH (2.5 mL). The solution was stirred at 55 °C for 13.5 h. Compound **5g** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a

yellow oil, 0.26 g, 59% yield; [Found: C, 75.0; H, 7.4; N, 8.5; S, 9.65. $C_{21}H_{24}N_2S$ requires C, 74.95; H, 7.2; N, 8.3; S, 9.5%]; ν_{max}(film) 3063, 3031, 2958, 2872, 1551, 1498, 1454, 1428, 1385, 1355, 1226, 1028, 911, 715 см$^{-1}$; δ_H (400 MHz, $CDCl_3$) 8.60 (1 H, d, *J* 1.5 Hz, H-2'), 8.48 (1 H, dd, *J* 4.9, 1.6 Hz, H-6'), 7.81 (1 H, ddd, *J* 7.8, 1.6, 1.5 Hz, H-4'), 7.31 (3 H, m, *m*-H, *p*-H), 7.28 (1 H, dd, *J* 7.8, 4.9 Hz, H-5'), 7.04 (2 H, d, *J* 7.1 Hz, *o*-H), 6.79 (1 H, s, H-5), 5.04 (2 H, s, NC$\underline{H}_2$), 2.34 (2 H, t, *J* 7.0 Hz, SC$\underline{H}_2$), 2.13 (3 H, s, Me), 1.35 (2 H, m, $SCH_2C\underline{H}_2$), 1.24 (2 H, m, $SCH_2CH_2C\underline{H}_2$), 0.78 (3 H, t, *J* 7.0 Hz, CH_3 (SBu)); δ_C (100.6 MHz, $CDCl_3$) 150.6 (C-6'), 146.8 (C-2'), 137.9 (C-4'), 137.4 (C-3'), 131.8 (C_i), 129.0 (C_o), 127.9 (C_p), 126.6 (C_m), 125.8 (C-5'), 123.0 (C-5), 121.5 (C-2), 116.3 (C-3), 111.1 (C-4), 51.0 (N$\underline{C}H_2$), 36.7 (S$\underline{C}H_2$), 31.4 ($SCH_2\underline{C}H_2$), 21.7 ($SCH_2CH_2\underline{C}H_2$), 13.8 ($CH_3$ (SBu)), 10.9 ($\underline{C}H_3$-C-2); δ_N (40.56 MHz, $CDCl_3$) -218.9, -74.3; GC-MS: *m/z* (%) 336 (85, M^+), 280 (47, M-$(CH_2)_4$), 247 (33, M-SBu), 189 (19), 94 (100, CH_2Ph).

*Benzylimine of (Z)-2-butylthio-3-(3-pyridyl)propenal (**6g**).* δ_H (400 MHz, $CDCl_3$) 8.78 (1 H, d, *J* 1.7 Hz, H-2'), 8.43 (1 H, dd, *J* 4.9, 1.6 Hz, H-6'), 8.33 (1 H, ddd, *J* 7.8, 1.7, 1.6 Hz, H-4'), 8.12 (1 H, s, CH=N), 7.38-7.23 (6H, m, *o*-H, *p*-H, *m*-H, H-5'), 7.19 (1 H, s, CH), 4.80 (2 H, s, NC$\underline{H}_2$), 2.83 (2 H, t, *J* 7.3 Hz, SC$\underline{H}_2$), 1.40 (2 H, m, $SCH_2C\underline{H}_2$), 1.22 (2 H, m, $SCH_2CH_2C\underline{H}_2$), 0.77 (3 H, t, *J* 7.3 Hz, CH_3 (SBu)).

*3-Benzylamino-2-butylthio-4-nitro-1-(3-pyridyl)pentene (**7g**).* 1,2-Adduct **7g** is a mixture of diastereomers in 2:1 ratio. δ_H (400 MHz, $CDCl_3$) 8.50 (1 H, d, *J* 1.6 Hz, H-2'), 8.43 (major) and 8.39 (minor) (1 H, dd, *J* 4.8, 1.7 Hz, H-6'), 7.77 (minor) and 7.70 (major) (1 H, dd, *J* 8.0, 1.7, 1.6 Hz, H-4'), 7.31-7.25 (6H, m, *o*-H, *p*-H, *m*-H, H-5'), 6.65 and 6.62 (minor), 6.55 and 6.53 (major) (1 H, s, CH=), 5.26 (1 H, m, HC*NO_2), 5.05 (minor) and 4.87 (major) (1 H, m, NH), 4.28 and 4.26 (1 H, s, $\underline{H}$C*NH), 4.21 (2 H, m, NCH_2), 2.11 and 1.92 (2 H, m, SCH_2), 1.41 (minor) and 1.37 (major) (3 H, d, *J* 6.6 Hz, CH$\underline{Me}$), 1.31-1.18 (4 H, m, $SCH_2C\underline{H}_2C\underline{H}_2$), 0.77 (3 H, 2 t, *J* 7.2 Hz, CH_3 (SBu)).

4.3.8. 1-Butyl-2-methyl-4-propylthio-3-(3-pyridyl)pyrrole (5h) was obtained by *method A* from (*Z*)-2-propylthio-3-(3-pyridyl)propenal (**4f**) (0.55 g, 2.6 mmol) butylamine (0.19 g, 2.6 mmol) and nitroethane (0.59 g, 7.9 mmol) in MeOH (2.5 mL). The solution was stirred at 55 °C for 5 h. Compound **5h** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.61 g, 80% yield; [Found: C, 70.5; H, 8.35; N, 9.9; S, 11.35. $C_{17}H_{24}N_2S$ requires C, 70.8; H, 8.4; N, 9.7; S, 11.1%]; ν_{max}(film) 3080, 3030, 2959, 2872, 1552, 1461, 1362, 1292, 1225, 1143, 1105, 1026, 715 см$^{-1}$; δ_H (400 MHz, $CDCl_3$) 8.55 (1 H, d, ^4J 1.6 Hz, H-2'), 8.47 (1 H, dd, ^3J 4.9, ^4J 1.6 Hz, H-6'), 7.77 (1 H, ddd, ^3J 7.8, ^4J 4.9, ^4J 1.6 Hz, H-4'), 7.30 (1 H, dd, ^3J 7.8, ^3J 4.9 Hz, H-5'), 6.74 (1 H, s, H-5), 3.80 (2 H, t, *J* 7.3 Hz, NC$\underline{H}_2$), 2.30 (2 H, t, *J* 7.2 Hz, SC$\underline{H}_2$), 2.21 (3 H, s, Me), 1.72 (2 H, m, $NCH_2C\underline{H}_2$), 1.38 (4 H, m, $C\underline{H}_2$Me (SPr, NBu)), 0.97 (3 H, t, *J* 7.3 Hz, CH_3 (SPr)), 0.80 (3 H, t, *J* 7.5 Hz, CH_3 (NBu)); δ_C (100.6 MHz, $CDCl_3$) 151.0 (C-6'), 147.0 (C-2'), 137.7 (C-4'), 132.0 (C-3'), 126.8 (C-2), 125.1 (C-5'), 123.0 (C-5), 121.1 (C-3), 110.4 (C-4), 47.0 (N$\underline{C}H_2$), 39.2 (S$\underline{C}H_2$), 33.4

($NCH_2\underline{C}H_2$), 22.6 ($SCH_2\underline{C}H_2$), 20.2 ($NCH_2CH_2\underline{C}H_2$), 13.9 ($CH_3$ in SPr), 13.5 (CH_3 (NBu)), 10.9 ($\underline{C}H_3$-C-2); GC-MS: *m/z* (%) 288 (100, M^+), 246 (59, M-$(CH_2)_3$), 213 (23, M-SPr), 171 (28), 148 (6).

*Butylimine of (Z)-2-propylthio-3-(3-pyridyl)propenal (**6h**).* δ_H (400 MHz, $CDCl_3$) 8.78 (1 H, s, H-2'), 8.45 (1 H, dd, *J* 4.6, 1.6 Hz, H-6'), 8.31 (1 H, dd, ^3J 8.0, ^4J 1.6 Hz, H-4'), 7.98 (1 H, s, CH=N), 7.32 (1 H, dd, *J* 8.0, 4.6 Hz, H-5'), 7.14 (1 H, s, HC=), 3.58 (2 H, t, *J* 7.3 Hz, $NC\underline{H}_2$ (NBu)), 2.83 (2 H, t, *J* 7.3 Hz, $SC\underline{H}_2$ (SPr)), 1.69 (2 H, m, $SCH_2C\underline{H}_2Me$), 1.47 (2 H, m, $NCH_2C\underline{H}_2$), 1.32 (2 H, m, $NCH_2CH_2C\underline{H}_2$), 0.94 (3 H, t, *J* 7.2 Hz, CH_3 in SPr), 0.86 (3 H, t, *J* 7.3 Hz, CH_3 in NBu).

*3-Butylamino-4-nitro-2-propylthio-1-(3-pyridyl)pentene (**7h**).* 1,2-Adduct **7h** is a mixture of diastereomers in 5:2 ratio. δ_H (400 MHz, $CDCl_3$) 8.50 (1 H, s, H-2'), 8.45 (major) and 8.39 (minor) (1 H, d, *J* 4.8 Hz, H-6'), 7.78 (minor) and 7.71 (major) (1 H, d, *J* 8.1 Hz, H-4'), 7.30 (major) and 7.22 (minor) (1 H, dd, *J* 8.1, 4.8 Hz, H-5'), 6.57 and 6.53 (minor), 6.44 and 6.41 (major) (1 H, s, =CH), 5.25 (1 H, m, HC^*NO_2), 4.61 (minor) and 4.51 (major) (1 H, m, NH), 3.85 and 3.82 (major), 3.84 and 3.81 (minor) (1 H, s, $\underline{H}C^*NH$), 3.12 (minor) and 3.05 (major) (2 H, m, NCH_2), 2.04 and 1.90 (2 H, m, SCH_2), 1.52 (6 H, m, $(CH_2)_3$ (SPr, NBu)), 1.39 (major) and 1.33 (minor) (3 H, d, *J* 7.0 Hz, $CH\underline{Me}$), 0.91 (3 H, t, *J* 7.2 Hz, Me in SPr), 0.82 (3 H, t, *J* 7.3 Hz, Me in NBu).

4.3.9. 1-Butyl-4-butylthio-2-methyl-3-(3-pyridyl)pyrrole (5i) was obtained analogously to **5h** by *method A* from butylamine (0.083 g, 1.1 mmol), (*Z*)-2-butylthio-3-(3-pyridyl)propenal (**4e**) (0.25 g, 1.1 mmol) and nitroethane (0.25 g, 3.4 mmol) in THF (1 mL). The solution was stirred at 55 °C for 15 h. Compound **5i** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.27 g, 80% yield; [Found: C, 71.4; H, 8.5; N, 9.15; S, 10.9. $C_{18}H_{26}N_2S$ requires C, 71.5; H, 8.7; N, 9.3; S, 10.6%]; ν_{max}(film) 3082, 3032, 2958, 2872, 1554, 1464, 1359, 1104, 1026, 714 $см^{-1}$; δ_H (400 MHz, $CDCl_3$) 8.56 (1 H, d, ^4J 1.4 Hz, H-2'), 8.47 (1 H, dd, ^3J 4.9, ^4J 1.6 Hz, H-6'), 7.78 (1 H, ddd, ^3J 7.8, ^4J 1.6, ^4J 1.4 Hz, H-4'), 7.29 (1 H, dd, ^3J 7.8, 4.9 Hz, H-5'), 6.72 (1 H, s, H-5), 3.81 (2 H, t, *J* 7.3 Hz, $NC\underline{H}_2$), 2.31 (2 H, t, *J* 7.1 Hz, $SC\underline{H}_2$), 2.21 (3 H, s, $\underline{Me}$), 1.73 (2 H, m, $SCH_2C\underline{H}_2$), 1.42-1.19 (6 H, m, $C\underline{H}_2Me$ (SBu, NBu)), 0.98 (3 H, t, *J* 7.3 Hz, CH_3 (BuS)), 0.76 (3 H, t, *J* 7.3 Hz, CH_3 (BuN)); δ_C (100.6 MHz, $CDCl_3$) 151.0 (C-6'), 150.3 (C-2'), 146.2 (C-4'), 131.8 (C-3'), 126.5 (C-2), 124.9 (C-5), 122.2 (C-5'), 120.7 (C-3), 110.3 (C-4), 46.6 ($N\underline{C}H_2$), 37.2 ($S\underline{C}H_2$), 33.3 ($NCH_2\underline{C}H_2Et$), 31.6 ($SCH_2\underline{C}H_2Et$), 21.2 ($NCH_2CH_2\underline{C}H_2CH_3$), 18.9 ($SCH_2CH_2\underline{C}H_2CH_3$), 13.4 ($CH_3$ (NBu)), 13.3 (CH_3 in SBu), 11.0 ($\underline{C}H_3$-C-2); δ_N (40.56 MHz, $CDCl_3$) -72.6, -215.2; GC-MS: *m/z* (%) 302 (100, M^+), 246 (53, M-$(CH_2)_4$), 213 (22, M-SBu), 171 (31), 148 (7).

*Butylimine of (Z)-2-butylthio-3-(3-pyridyl)propenal (**6i**).* δ_H (400 MHz, $CDCl_3$) 8.79 (1 H, d, *J* 1.6 Hz, H-2'), 8.49 (1 H, dd, ^3J 4.8, ^4J 1.7 Hz, H-6'), 8.29 (1 H, ddd, ^3J 8.0, ^4J 1.7, ^4J 1.6 Hz, H-4'), 7.98 (1 H, HC=N), 7.30 (1 H, dd, ^3J 8.0, ^3J 4.8 Hz, H-5'), 7.12 (1 H, s, CH), 3.59 (2 H, t, *J* 6.8 Hz, $NC\underline{H}_2$), 2.84 (2 H, t, *J* 7.3 Hz, $SC\underline{H}_2$), 1.67 (2 H, m, $NCH_2C\underline{H}_2$), 1.53-1.35 (6 H, m, $(CH_2)_3$ (SBu, NBu)), 0.96 (3 H, t, *J* 7.2 Hz, CH_3 (SBu)), 0.84 (3 H, t, *J* 7.3 Hz, CH_3 (BuN)).

*3-Butylamino-2-butylthio-4-nitro-1-(3-pyridyl)pentene (**7i**).* 1,2-Adduct **7i** is a mixture of diastereomers in 1.5:1 ratio. δ_H (400 MHz, $CDCl_3$) 8.53 (1 H, d, *J* 1.6 Hz, H-2'), 8.48 (major) and 8.43 (minor) (1 H, dd, ^3J 4.8 Hz, ^4J 1.7 Hz, H-6'), 7.72 (minor) and 7.66 (major) (1 H, ddd, ^3J 8.0, ^4J 1.7, ^4J 1.6 Hz, H-4'), 7.24 (major) and 7.19 (minor) (1 H, dd, ^3J 8.0 Hz, ^3J 4.8 Hz, H-5'), 6.56 and 6.53 (minor), 6.44 and 6.41 (major) (1 H, s, HC=), 5.23 (1 H, m, HC*NO_2), 4.61 (minor) and 4.51 (major) (1 H, m, NH), 3.83 and 3.80 (1 H, s, HC*NH), 3.07 (minor) and 3.02 (major) (2 H, m, NCH_2), 2.05 and 1.91 (2 H, m, SCH_2), 1.49 (minor) and 1.41 (major) (3 H, d, *J* 6.6 Hz, CH_3), 1.47-1.21 (8 H, $(CH_2)_4$ (SBu, NBu)), 0.90 (3 H, t, *J* 7.2 Hz, Me in SBu), 0.86 (3 H, t, *J* 7.3 Hz, Me in NBu).

4.3.10. 1-Butyl-4-butylthio-2-methyl-3-(2-nitrophenyl)pyrrole (5j) was obtained by *method B* from butylamine (0.095 g, 1.3 mmol), (*Z*)-2-butylthio-3-(2-nitrophenyl)propenal (**4g**) (0.346 g, 1.3 mmol) and nitroethane (0.29 mg, 3.9 mmol) in MeOH (1 mL). The solution was stirred at 55 °C for 14 h. Compound **5j** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as brown oil, 0.34 g, 60% yield; [Found: C, 65.8; H, 7.3; N, 7.95; S, 9.4. $C_{19}H_{26}N_2OS$ requires C, 65.9; H, 7.6; N, 8.1; S, 9.25%]; ν_{max}(film) 2931, 2872, 1554, 1525, 1456, 1353, 1115, 853, 750 см$^{-1}$; δ_H (400 MHz, $CDCl_3$) 7.82 (1 H, d, *J* 8.2 Hz, H-3'), 7.52 (1 H, dd, *J* 7.8, 7.5 Hz, H-5'), 7.38 (1 H, d, *J* 7.8 Hz, H-6'), 7.36 (1 H, dd, *J* 8.2, 7.5 Hz, H-4'), 6.67 (1 H, s, H-5), 3.74 (2 H, t, *J* 7.3 Hz, $NC\underline{H}_2$), 2.24 (2 H, m, $SC\underline{H}_2$), 2.00 (3 H, s, Me), 1.69-1.22 (8 H, 2m, $C\underline{H}_2$Me (SBu, NBu)), 0.92 (3 H, t, *J* 7.6 Hz, CH_3 (BuN)), 0.72 (3 H, t, *J* 6.8 Hz, CH_3 (SBu)); δ_C (100.6 MHz, $CDCl_3$) 150.6 (C-1'), 134.5 (C-4'), 131.7 (C-5'), 130.7 (C-2'), 127.4 (C-6'), 127.0 (C-2), 125.0 (C-5), 123.9 (C-3'), 120.2 (C-3), 110.2 (C-4), 46.9 ($N\underline{C}H_2$), 36.5 ($S\underline{C}H_2$), 33.1 ($NCH_2\underline{C}H_2$), 31.4 ($SCH_2\underline{C}H_2$), 21.6 ($NCH_2CH_2\underline{C}H_2$), 19.9 ($SCH_2CH_2\underline{C}H_2$), 13.8 ($CH_3$ (NBu)), 13.6 (CH_3 (SBu)), 10.6 ($\underline{C}H_3$-C-2); GC-MS: m/z (%) 346 (100, M^+), 257 (7, M-SBu), 200 (28).

In spectra ^{15}N NMR the cross peak (-215.6 ppm) of the pyrrole ring nitrogen atom with the protons of CH_3-group, NCH_2 fragment and the proton H-5 is observed. Also the cross peak (-2.6 ppm) of the NO_2-group nitrogen atom and the proton H-3 'of the phenyl ring is seen.

*3-Butylamino-2-butylthio-4-nitro-1-(2-nitrophenyl)pentene (**7j**).* 1,2-Adduct **7j** is a mixture of diastereomers in 15:1 ratio. δ_H (400 MHz, $CDCl_3$) 7.78 (1 H, d, *J* 8.2 Hz, H-3'), 7.65 (1 H, d, *J* 7.7 Hz, H-6'), 7.55 (1 H, t, *J* 7.7 Hz, H-5'), 7.38 (1 H, t, *J* 8.2 Hz, H-4'), 6.44 and 6.41 (1 H, s, CH=), 5.27 (1 H, m, HC*NO_2), 4.62 (1 H, m, NH), 4.57 and 4.55 (1 H, s, HC*NH), 3.03 (2 H, m, NCH_2), 2.00 (2 H, m, SCH_2), 1.43 (3 H, d, *J* 6.6 Hz, CH_3), 1.32-1.21 (8 H, m, $(CH_2)_4$ (SBu, NBu)), 0.90 (3 H, t, *J* 7.2 Hz, Me in SBu), 0.79 (3 H, t, *J* 7.3 Hz, Me in NBu).

4.3.11. 1-Butyl-4-hepthylthio-2-methyl-3-(4-nitrophenyl)pyrrole (5k) was obtained by *method B* from butylamine (0.071 g, 0.98 mmol), (*Z*)-2-butylthio-3-(4-nitrophenyl)propenal (**4h**) (0.3 g, 0.98 mmol) and nitroethane (220 mg, 2.93 mmol) in MeOH (1 mL). The solution was stirred at 55 °C for 14 h. Compound **5k** was isolated by column chromatography on silica gel (elution with CH_2Cl_2) as a brown oil, 0.25 g, 67% yield; [Found: C, 68.1; H, 8.1; N, 7.2; S, 8.2. $C_{22}H_{32}N_2OS$ requires C, 68.0; H, 8.3; N,

7.2; S, 8.25%.]; ν_{max}(film) 2927, 2855, 1595, 1551, 1516, 1457, 1384, 1340, 1109, 854, 702 см$^{-1}$; δ_H (400 MHz, $CDCl_3$) 8.23 (2 H, d, *J* 8.3 Hz, H-3',5'), 7.58 (2 H, d, *J* 8.3 Hz, H-2',6'), 6.75 (1 H, s, H-5), 3.82 (2 H, t, *J* 7.2 Hz, NC$\underline{H}_2$), 2.35 (2 H, t, *J* 7.3 Hz, SC$\underline{H}_2$), 2.24 (3 H, s, Me), 1.72-1.13 (14 H, 2m, C$\underline{H}_2$ (SHept, NBu)), 0.97 (3 H, t, *J* 7.3 Hz, CH_3 (NBu)), 0.84 (3 H, t, *J* 7.1 Hz, CH_3 (SHept); δ_C (100.6 MHz, $CDCl_3$) 145.7 (C-1'), 143.3 (C-4'), 130.5 (C-2', 6'), 127.4 (C-2), 125.3 (C-5), 123.3 (C-3', 5'), 122.5 (C-3), 110.3 (C-4), 46.9 (N$\underline{C}H_2$), 37.1 (S$\underline{C}H_2$), 33.1 (NCH$_2\underline{C}H_2$), 31.7 (SCH$_2\underline{C}H_2$), 29.2 (SCH$_2$CH$_2\underline{C}H_2$), 28.9 (SCH$_2$CH$_2$CH$_2\underline{C}H_2$), 28.5 (S(CH$_2$)$_4\underline{C}H_2$), 22.6 (NCH$_2$CH$_2\underline{C}H_2$), 20.0 (S(CH$_2$)$_5\underline{C}H_2$), 14.0 (CH_3 (SHept), 13.8 (CH_3 (NBu)), 11.0 ($\underline{C}H_3$-C-2); GC-MS: *m/z* (%) 388 (91, M^+), 290 (100, M-(CH$_2$)$_7$), 257 (28, M-SHept), 233 (4), 200 (23).

In spectra ^{15}N NMR the cross peak (-214.2 ppm) of the pyrrole cycle nitrogen atom with the protons of CH_3-group, NCH_2 fragment and the proton H-5 is observed. Besides the cross peak (-8.3 ppm) of the NO_2-group nitrogen atom and the phenyl cycle protons H-3' and H-5' is seen.

*3-Butylamino-2-hepthylthio-4-nitro-1-(4-nitrophenyl)pentene (**7k**).* 1,2-Adduct **7k** is a mixture of diastereomers in 2:1 ratio. δ_H (400 MHz, $CDCl_3$) 8.16 (major) and 8.11 (minor) (2 H, d, *J* 8.7 Hz, H-3',5'), 7.51 (minor) and 7.47 (major) (2 H, d, *J* 8.7 Hz, H-2',6'), 6.57 and 6.54 (minor), 6.46 and 6.43 (major) (1 H, s, CH=), 5.25 (1 H, m, HC*NO_2), 4.62 (1 H, m, NH), 3.91 and 3.88 (major), 3.87 and 3.85 (minor) (1 H, s, $\underline{H}$C*NH), 3.10 (minor) and 3.07 (major) (2 H, m, NCH_2), 2.06 and 1.91 (2 H, m, SCH_2), 1.37 (minor) and 1.34 (major) (3 H, d, *J* 6.6 Hz, CH_3), 1.31-1.16 (14 H, $(CH_2)_7$ (SHept, NBu)), 0.92 (3 H, t, *J* 7.2 Hz, Me in SHept), 0.86 (3 H, t, *J* 7.3 Hz, Me in NBu).

4.4. General synthesis of 3-aryl(hetaryl)-2-substituted enals 4c, d, f-h

*4.4.1. (Z)-2-Propylthio-3-(2-furyl)propenal (**4c**)* was obtained by a known method.[27] Clear dark-orange liquid, 1.1 g, 63% yield, after column chromatography on silica gel (elution with hexane / ether 3 : 1); [Found: C, 61.1; H, 6.3; S, 16.1. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.2; S, 16.3%]; ν_{max} (film) 2961, 2927, 2872, 2854, 1686 (C=O), 1586 (C=C), 1466, 1197, 1115, 1020, 941, 885, 751 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.48 (1 H, s, CHO), 7.61 (1 H, d, *J* 1.2 Hz, H-5), 7.51 (1 H, d, *J* 3.5 Hz, H-3), 7.42 (1 H, s, =CH), 6.59 (1 H, dd, *J* 3.5, 1.2 Hz, H-4), 3.00 (2 H, t, *J* 7.3 Hz, SCH_2), 1.57 (2 H, m, CH_2), 0.95 (3 H, t, *J* 7.3 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 190.1 (CHO), 151.0 (C-2), 145.4 (C-5), 137.5 (=CH), 132.5 (=C-S), 118.2 (C-3), 113.2 (C-4), 34.0 (SCH_2), 23.7 (CH_2), 13.3 (CH_3); GC-MS: *m/z* (%) 196 (100, M^+), 167 (20, M^+-CHO), 125 (35), 97 (52).

*4.4.2. (Z)-2-Heptylthio-3-(2-furyl)propenal (**4d**)* was obtained by a known method.[27]

Clear brown liquid, 1.06 g, 59% yield, after column chromatography on silica gel (elution with hexane / ether 3 : 1); [Found: C, 66.9; H, 8.15; S, 13.1. $C_{14}H_{20}O_2S$ requires C, 66.6; H, 8.0; S, 12.7%]; ν_{max} (film) 2929, 2857, 1684 (C=O), 1587 (C=C), 1467, 1199, 1116, 1021, 908, 789, 763, 734 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.48 (1 H, s, CHO), 7.61 (1 H, d, *J* 1.4 Hz, H-5), 7.50 (1 H, d, *J* 3.5 Hz, H-3), 7.42 (1 H,

s, =CH), 6.59 (1 H, dd, *J* 3.5, 1.4 Hz, H-4), 3.00 (2 H, t, *J* 7.3 Hz, SCH_2), 1.54 (2 H, m, CH_2), 1.24 (8 H, m, $(CH_2)_4$), 0.86 (3 H, t, *J* 7.0 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 190.1 (CHO), 151.0 (C-2), 145.3 (C-5), 137.4 (=CH), 136.1 (=C-S), 118.2 (C-3), 113.2 (C-4), 32.1 (SCH_2), 31.7 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); GC-MS: *m/z* (%) 252 (100, M^+), 223 (6, M^+-CHO), 167 (12, M^+-CHO-$(CH_2)_4$), 154 (39), 122 (39), 97 (44), 81 (30), 66 (9), 55 (15), 41 (24), 29 (11, CHO).

*4.4.3. (Z)-2-Propylthio-3-(3-pyridyl)propenal (**4f**)* was obtained by a known method.[27] Clear dark-orange liquid, 1.96 g, 45% yield, after column chromatography on silica gel (elution with hexane / ether / acetone 2 : 1: 1); [Found: C, 63.7; H, 6.3; N, 6.55; S, 15.7. $C_{11}H_{13}NOS$ requires C, 63.8; H, 6.3; N, 6.7; S, 15.5%]; ν_{max} (film) 2962, 2931, 2871, 1692 (C=O), 1590 (C=C), 1561, 1461, 1417, 1115, 1024, 803, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.60 (1 H, s, CHO), 8.93 (1 H, d, *J* 1.6 Hz, H-2), 8.60 (1 H, dd, *J* 4.9, 1.6 Hz, H-6), 8.46 (1 H, d, *J* 8.0 Hz, H-4), 7.53 (1 H, s, =CH), 7.39 (1 H, dd, *J* 8.0, 4.9 Hz, H-5), 2.96 (2 H, t, *J* 7.3 Hz, SCH_2), 1.55 (2 H, m, CH_2), 0.92 (3 H, t, *J* 7.3 Hz, CH_2); δ_C (100.6 MHz, $CDCl_3$) 190.7 (CHO), 152.1 (C-6), 150.7 (C-2), 146.7 (C-4), 138.7 (=C-S), 137.1 (C-5), 130.3 (C-3), 123.2 (=CH), 34.4 (overlapping of chemical shifts SCH_2- and CH_2- groups), 23.4 (SCH_2), 13.1 (CH_3); GC-MS: *m/z* (%) 221 (53) [M^+], 188 (27), 174 (10), 164 (59), 148 (15), 136 (100).

*4.4.4. (Z)-2-Butylthio-3-(2-nitrophenyl)propenal (**4g**)* was obtained by a known method.[27] Clear brown liquid, 0.88 g, 38% yield, after column chromatography on silica gel (elution with hexane / ether 2 : 1); [Found: C, 58.64; H, 5.51; N, 5.00; S, 12.1; $C_{13}H_{15}NO_3S$ requires C, 58.87; H, 5.66; N, 5.28; S, 12.07%]; ν_{max} (film) 2959, 2930, 1695 (C=O), 1568 (C=C), 1343, 1119, 864, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.68 (1 H, s, CHO), 8.19 (1 H, d, *J* 8.1 Hz, H-3), 7.98 (1 H, s, =CH), 7.70 (1 H, dd, *J* 8.4, 7.4 Hz, H-5), 7.62 (1 H, d, *J* 7.4 Hz, H-6), 7.57 (1 H, dd, *J* 8.4, 8.1 Hz, H-4), 2.80 (2 H, t, *J* 7.5 Hz, SCH_2), 1.39 (2 H, m, CH_2), 1.24 (2H, m, CH_2), 0.81 (3 H, t, *J* 7.5 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 190.6 (CHO), 147.5 (=CH), 147.3 (C-2), 139.4 (=C-S), 133.3 (C-5), 131.7 (C-6), 130.4 (C-1), 130.2 (C-4), 125.0 (C-3), 32.0 (SCH_2), 31.9 (CH_2), 21.7 (CH_2), 13.6 (CH_3); GC-MS: *m/z* (%) 265 (1, M^+), 248 (3), 236 (13, M^+-CHO), 220 (7), 208 (35), 176 (26), 164 (24), 152 (71), 132 (32), 120 (69), 104 (15), 92 (100), 77 (28), 65 (30), 57 (22), 41 (40), 29 (40, CHO).

*4.4.5. (Z)-2-Heptylthio-3-(4-nitrophenyl)propenal (**4h**)* was obtained by a known method.[27] Clear brown liquid, 2.93 g, 89% yield; [Found: C, 62.22; H, 6.81; N, 4.50; S, 10.33. $C_{16}H_{21}NO_3S$ requires C, 62.54; H, 6.84; N, 4.56; S, 10.42%.]; ν_{max} (film) 2955, 2927, 2855, 1695 (C=O), 1602, 1521 (C=C), 1345, 1124, 1105, 863, 853, 750, 687 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.62 (1 H, s, CHO), 8.26 (2 H, d, *J* 9.1 Hz, H-3,5), 8.01 (2 H, d, *J* 9.1 Hz, H-2,6), 7.57 (1 H, s, =CH), 2.99 (2 H, t, *J* 7.5 Hz, SCH_2), 1.53 (2 H, m, CH_2), 1.42-1.15 (8 H, m, CH_2), 0.86 (3 H, t, *J* 6.8 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 190.9 (CHO), 147.9 (C_i), 146.5 (=CH), 140.5 (C-NO_2), 140.3 (=C-S), 131.5 (C-2,6), 123.8 (C-3,5), 32.5 (SCH_2), 31.6 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3); GC-MS: *m/z* (%)

307 (100 M^+), 290 (30), 277 (10), 260 (11), 236 (8), 222 (10), 208 (23), 192 (76), 176 (30), 162 (44), 147 (23), 134 (48), 115 (11), 89 (47), 57 (64), 41 (72), 27 (14).

References

1. (a) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517; (b) Young, I. S.; Thornton, P.D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.

2. (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264; (b) Fucuda, T.; Ishibashi, F.; Iwao, M. *Heterocycles*. **2011**, *83*, 491 (review).

3. (a) Chen, G.; Wang, H.-F.; Pei, Y.-H. *J. Asian Natur. Products Res.* **2013,** *16*, 105; (b) Demopoulos, V. J.; Rekka, E. *J. Pharm. Sciences* **1995**, *84*, 79.

4. (a) Raimondi, M. V.; Cascioferro, S.; Schillaci, D.; Petruso, S. *Eur. J. Med. Chem*. **2006**, *41*, 1439; (b) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep.* **2011**, *28*, 1229; (c) Bürli, R. W.; McMinn, D.; Kaizerman, J. A.; Hu, W.; Ge, Y.; Pack, Q.; Jiang, V.; Gross, M.; Garcia, M.; Tanaka, R.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1253; (d) Joshi, S. D.; Vagdevi, H. M.; Vaidya, V. P.; Gadaginamath, G. S. *Eur. J. Med. Chem.* **2008**, *43*, 1989; (e) Pacorel, B., Leung, S. C., Stachulski, A. V., Davies, J., Vivas, L., Lander, H., Ward, S. A., Kaiser, M., Brun, R., O'Neill, P. M. *J. Med. Chem*. **2010**, *53*, 633.

5. (a) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S.; Tidwell, R. R.; Czarny, A.; Bajic, M.; Bajic, M.; Kumar, A.; Boykin, D.; Perfect, J. R. *Antimicrobial Agents and Chemotherapy* **1998**, *42*, 2495; (b) Wang, M.-Z.; Xu, H.; Liu, T.-W.; Feng, Q.; Yu, S.-J.; Wang, S.-H.; Li, Z.-M. *Eur. J. Med. Chem.* **2011**, *46*, 1463.

6. (a) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, 34, 991; (b) Wang, D.; Hu, X.; Zhao, G. *Int. J. Food Sci. Technol.* **2008**, *43*, 1880.

7. (a) Pinna, G. A.; Loriga, G.; Murineddu, G.; Grella, G.; Mura, M.; Vargiu, L.; Murgioni, C.; La Colla, P. *Chem. Pharm. Bull.* **2001**, *49***,** 1406; ; (b) Holmes, R. T.; Lu, J.; Mwakwari, C.; Smith, K. M. *Arkivoc* **2010** (v), 5; (c) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Loi A. G.; Scintu, F.; Milia, C.; Puddu, I.; La Colla, P. *II Farmaco* **1998**, *53*, 33; (d) Boonlarppradab, C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 5505.

8. (a) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090; (b) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861; (c) Kim, D.-M.; Kim, M.-Y.; Reddy, S. S.; Cho, J.; Cho, C.; Jung, S.; Shim, Y.-B. *Anal. Chem.* **2013**, *85*, 11643; (d) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213; (e) Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa,

J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446.

9. (a) Idhayadhulla, A.; Kumar, R. S.; Nasser, A. J. A.; Manilal, A. *Bull. Chem. Soc. Ethiop.* **2012**, *26*, 429; (b) Hughes, C. C., Prieto-Davo, A., Jensen, P. R., Fenical, W. *Org. Lett.* **2008**, *10*, 629; (c) Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafi, A.; Manetti, F. *Bioorg. Med. Chem.* **2004**, *12*, 1453; (d) Biava, M.; Porretta, G. C.; Poce, G.; De Logu, A.; Saddi, M.; Meleddu, R.; Manetti, F.; De Rossi, E.; Botta, M. *J. Med. Chem.* **2008**, *51*, 3644; (e) Padrón, J. M.; Tejedor, D.; Santos-Expósito, A.; García-Tellado, F.; Martín, V. S.; Villar, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2487; (f) Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479; (g) Burnham, B. S.; Gupton, J. T.; Krumpe, K.; Webb, T.; Shuford, J.; Bowers, B.; Warren, A. E.; Barnes, C.; Hall, I. H. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 337; (h) Arthur, C. R.; Gupton, J. T.; Kellogg, G. E.; Yeudall, W. A.; Cabot, M. C.; Newsham, I. F.; Gewirtz, D. A. *Biochem. Pharmacol.* **2007**, *74*, 981; (i) Khan, A. T.; Lal, M.; Bagdi, P. R.; Basha, R. S.; Saravanan, P.; Patra, S. *Tetrahedron Lett.* **2012**, *53*, 4145.

10. (a) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891; (b) Schutting, S.; Borisov, S. M. *Anal. Chem.* **2013**, *85*, 3271;

11. Ye, Z.; Shi, L.; Shao, X.; Xu, X.; Li, Z. *J. Agric. Food Chem.* **2013**, *61*, 312;

12. (a) Mack, J.; Kobayashi, N. *Chem. Rev.* **2011**, *111*, 281; (b) Wood, T. E.; Thompson, A. *Chem. Rev.* **2007**, *107*, 1831; (c) Sobenina, L. N.; Vasil'tsov, A. M.; Petrova, O. V., Petrushenko, K. B., Ushakov, I. A., Clavier, G., Meallet-Renault, R., Mikhaleva, A. I., Trofimov, B. A. *Org. Lett.* **2011**, *13*, 2524; (d) Schmidt, E. Yu.; Zorina, N. V.; Dvorko, M. Yu., Protsuk, N. I., Belyaeva, K. V., Clavier, G., Méallet-Renault, R., Vu, T. T., Mikhaleva, A. I., Trofimov, B. A. *Chem. Eur. J.* **2011**, *17*, 3069; (e) Zhang, M.; Hao, E.; Xu, Y.; Zhang, S.; Zhu, H.; Wang, Q.; Yu, C.; Jiao, L. *RSC Advances* **2012**, *2*, 11215; (f) Han, T.; Feng, X.; Shi, J.; Tong, B.; Dong, Y.; Lam, J. W. I.; Dong, Y.; Tang, B. Z. *J. Mater. Chem. C.* **2013**, *1*, 7534; (g) Li, Q.; Shi, J.; Li H.; Li, S.; Zhong, C., Guo, F.; Peng, M.; Hua, J.; Qin, J.; Li, Z. *J. Mater. Chem.* **2012**, *22*, 6689.

13. (a) Bhat, S. I.; Trivedy, D. R. *Tetrahedron Lett.* **2013**, *54*, 5577; (b) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Yu.; Sobenina, L. N. in *Advances in Heterocyclic Chemistry*, ed. Katritzky A. R., Academic Press, San Diego, 2010, vol. 99, pp. 209; (c) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Yu.; Sobenina, L. N. Chemistry of pyrrole: New papers, Nauka, Novosibirsk, **2012**, 383; (d) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Synthesis* **2013**, *45*, 93; (e) Agraval, S.; Pässler, U.; Knölker, H.-J. *Arkivoc* **2013** (ii), 6; (f) Das, B., Bhunia, N.; Lingaiah, M. *Synthesis* **2011**, 3471; (g) Li, B. C.; Montgomery, D. C.; Puckett, J. W.; Dervan, P. B. *J. Org. Chem.* **2013**, *78*, 124; (h) Cheng, P.; Shao, W.; Clive, D. L. *J. Org. Chem.* **2013**, *78*, 11860; (i) Yan, R.; Kang, X.; Zhou, X.; Li, X.; Liu, X.; Xiang, L.; Li, Y.; Huang, G. *J. Org. Chem.* **2014**, *79*, 465; (j) Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Peňa-López, M.; Ley, V. *Org. Biomol. Chem.*

2012, *10*, 5774; (k) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 4012; (l) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 6958.

14. (a) Silveira, C. C.; Mendes, S. R.; Martins, G. M.; Schlösser, S. C.; Kaufman, T. S. *Tetrahedron* **2013**; *69*, 9076; (b) Yoshida, M.; Sugimura, C. *Tetrahedron Lett.* **2013**, *54*, 2082; (c) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674; (d) Ren, C.-Q., Di, C. H.; Zhao, Y.-L.; Zhang, J.-P. *Tetrahedron Lett.* **2013**, *54*, 1478; (e) Tammadon, F.; Farani, M.; Karami, B. *J. Molecular Cat. A: Chemical* **2012**, *356*, 85; (f) Ng, E. P. J.; Wang, Y.-F.; Hui, B. W.-Q.; Lapointe, G.; Chibo, S. *Tetrahedron* **2011**, *67*, 7728; (g) Yavari, J.; Ghazvini, M.; Azad L.; Sanaeishoar, T. *Chinese Chem. Lett.* **2011**, *22*, 1219; (h) Magar, D. R.; Ke, Y.- J.; Chen, K. *Asian J. Org. Chem.* **2013**, *2*, 330; (i) Zhao, M.; Wang, F.; Li, X. *Org. Lett.* **2012**, *14*, 1412; (j) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146; (k) Tamaddom, F.; Amirpoor, F. *Synlett* **2013**, *24*, 1791; (l) Yavari, I.; Bayat, M. *Synlett* **2013**, *24*, 2591; (m) Atar, A. B.; Jeong, Y. T. *Tetrahedron Lett.* **2013**, *54*, 5624.

15. For review, see: (a) Estervez, V.; Villacampa, M.; Menerndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402; for recent selected examples, see: (b) Estervez, V.; Villacampa, M.; Menerndez, J. C. *Chem. Commun.* **2013**, *49*, 591; (c) Nandeesh, K. N.; Raghavendra, G. M.; Revanna, C. N.; Vijay, T. A. J.; Rangappa, K. S.; Mantelingu, K. *Synth. Commun.* **2014**, *44*, 1103.

16. (a) Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem*. **1998**, *63*, 6234; (b) Ranu, B. C.; Hajra, A.; Jana, U. *Synlett* **2000**, 75; (c) Ranu, B. C.; Hajra, A. *Tetrahedron* **2001**, *57*, 4767.

17. Keiko, N. A.; Aksamentova, T. N.; Chipanina, N. N.; Verochkina, E. A.; Vchislo, N. V. *Tetrahedron* **2013**, *69*, 2022;

18. Xiao, Y. S.; Wang, Y. G. *Chin. Chem. Lett.* **2003**, *14*, 893.

19. a) Deschamps, B; Anh, N. T.; Seyden Penne, J. *Tetrahedron Lett.* **1973**, *14*, 527; b) Sauvetre, R.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron* **1978**, *34*, 2135; c) Wartski, L.; El-Bouz, M.; Seyden-Penne, J. *J. Organomet. Chem.* **1979**, *177*, 17; d) Quick, J.; Jenkins, R. *J. Org. Chem.* **1978**, *43*, 2275; e) Hűnig, S.; Schäfer, M.; Schweeberg, W. *Chem. Ber*. **1993**, *126*, 205;

20. Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Comm.* **2009**, 874;

21. a) Espinosa, M.; Blay, G.; Cardona, L.; Pedro, J.R. *Chem. Eur. J.* **2013**, *19*, 14861; b) Geirsson, J. K. F.; Gudmundsdottir, A. D. *Acta Chem. Sand.* **1989**, *43*, 618;

22. a) Zhang, F.; Liu, Z.-J.; Liu, J. T. *Org. Biomol. Chem.* **2011**, *9*, 3625; b) Palacios, F.; Ochoade Retana, A. M.; Pascual, S.; Fernández de Trocóniz, G. *Tetrahedron* **2011**, *67*, 1575;

23. a) Yanovskaya, L.A.; Kryshtal', G. V.; Kul'ganek, V. V. *Russ. Chem. Rev*. **1984**, *53*, 744; b) Kryshtal', G. V.; Serebryakov, E. P. *Russ. Chem. Bull.* **1995**, *44*, 1785; c) Perlmutter, P. Conjugate Addition Reactions in Organic Synthesis; Pergamon Press: Oxford, **1992**; d) Keiko, N. A.; Chuvashev, Yu. A.; Kuznetsova, T. A.; Sherstyanikova, L. V.; Voronkov, M. G. *Russ. Chem. Bull.* **1998**, *47*, 2426;

24. a) Shen, X.; Ni, C.; Hu, J. *Helv. Chim. Acta* **2012**, *95*, 2043; b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2006**, *105*, 933;

25. a) Wartski, L.; El Bouz, M. *Tetrahedron* **1982**, *38*, 3285; b) Luchetti, J.; Krief, A. *J. Organomet. Chem*. **1980**, *194*, 49; El Bouz, M.; Wartski, L. *Tetrahedron Lett*. **1980**, *21*, 2897;

26. a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, 56, 8033; b) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1570; c) Pal, R.; Sarkaz, T.; Khashobis, S. *Arkivoc* **2012**, (*i*), 570.

27. Keiko, N. A.; Stepanova, L. G.; Verochkina, E. A.; Larina, L. I. *Arkivoc* **2010**, (*ii*), 49.