Synthesis and properties of 2-alkoxy- and 2-alkylthio-
-3-aryl(hetaryl)propenals

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Abstract

2-Alkoxy- and 2-alkylthio-3-aryl(hetaryl)propenals have been synthesized in 57-84% yields by the reaction of aldol condensation of aryl(hetaryl) aldehydes with 2-alkoxy- and 2-butylthioacetaldehydes. In the presence of alkali catalysts the reaction proceeds stereoselectively in two-phase systems. The direction of the C=C bond hydration of the prepared enals in the course of hydrolysis in acidic medium has been investigated.

Keywords: Aldehydes, aldol condensation, two-phase systems, conjugation, capto-dative substituents, hydrolysis

Introduction

The introduction of functional groups at the α-position of α,β-unsaturated carbonyl compounds represents an important synthetic problem.[1] The chemistry of 2-functionally substituted alkenals is rich and diverse.[2] For example, α-alkoxy-[3] and α-alkylthioacroleins [4,5] are important starting reagents in the synthesis of medical drugs. Aliphatic 2-alkoxy- and 2-alkylthioalkenals have been synthesized using a number of different protocols.[2,6] The most common procedure involves the aminomethylation of the corresponding alkoxy- or aryloxyacetaldehydes followed by the decomposition of hydrochloride Mannich base.[7] The attempts to prepare 2-alkylthiopropenals by either Mannich reaction[8] or alkylsulfenylchlorination of acrolein with subsequent dehydrochlorination of the adduct[9] almost always result in the isolation of cyclic dimers, namely 2-formyl-2,5-dialkylthio-2,3-dihydro-4*H*-pyranes. Unlike 3-unsubstituted 2-alkylthiopropenals, 3-methyl- or 3,3-dimethyl-2-alkylthiopropenals exist in monomeric forms. The former are easily synthesized by the reaction of *ipso*-substitution of bromine in 2-bromo-2-butenal,[10] and the latter are prepared by a reaction of 1-ethoxy-3-methylbut-1-yn-3-ol with ethanethiol in the presence of a peroxide, followed by acid catalyzed rearrangement. [11]

Methods for the preparation of more sterically hindered 3-aryl-2-methoxypropenals are scarce in number. It was reported that the Wittig reaction of triphenyl-(methoxy formyl methylidene)phosphorane with aromatic aldehydes furnishes the target enals **1** in 50-70% yields[12] (Scheme 1).

R = Ph, 2-NO$_2$C$_6$H$_4$
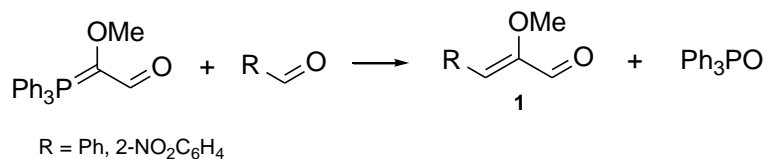
Scheme 1. Synthesis of 3-aryl-2-methoxyalkenals by Wittig reaction.

2-Methoxy- and 2-ethoxy-3-phenylpropenals were synthesized by the aldol condensation of benzaldehyde with methoxy- and ethoxyacetaldehydes in only 20 and 15% yields, respectively.[13]

The synthesis of heteroaromatic 2-alkoxy- and 2-alkylthio-2-alkenals, to the best of our knowledge, has not been reported previously. However, it was briefly mentioned that 4-alkyl-3-phenylthio-3-butene-2-ones **4** were obtained by the reaction of phenylthioacetone **2** with aldehydes **3** (R groups were not specified) [14] (Scheme 2).
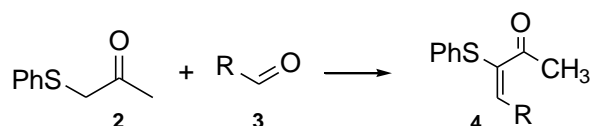

Scheme 2. Synthesis of 4-alkyl-3-phenylthio-3-butene-2-ones by the reaction of aldol condensation of phenylthioacetone with aldehydes.

This protocol, in the authors opinion, was acknowledged to be not suitable for the large-scale syntheses due to the low yields, polymerization and appearance of byproducts. Besides, the ketones were also indicated to be highly prone to cyclodimerization through the Diels-Alder reaction (20 °C, 30 h).

The conclusions made in this work point to *a priori* unexpected difficulties of the reaction in the case of application of more reactive α-alkylthioacetaldehydes where apart from the above side reactions, their self-condensation is also possible.

All the title aldehydes represent an interest as highly reactive functionalized analogs of cinnamaldehyde[15] or 2-alkyl-3-hetaryl propenals,[16] widely used in organic synthesis. The remarkable chemical feature of several 2-alkoxy-3-aryl(hetaryl)propenals (or their acetals, imines, hydrazones, and other derivatives) could be an opportunity of acidic hydrolysis of the double bond according to the Markovnikov rule. For instance, in the case of 2-alkoxypropenals[17] the reaction leads to methylglyoxal, a renowned metabolite and low-molecular weight regulator of cells growth.[18] Such direction of 2-alkoxy-3-arylpropenals hydrolysis could open the way to aryl(hetaryl)glyoxals. The possibility of regioselective reaction of acidic hydrolysis affording

1,2-diketones or α-ketoacids **6** (Scheme 3) has been already proved on the example of hydrolysis of ketones and esters of acids **5**. The latter are similar to aldehydes **1**, the hydrolysis of which has not been studied yet.[12]


$R^1 = C_6H_5$, $2\text{-}NO_2C_6H_4$
$R = CH_3$, OC_2H_5
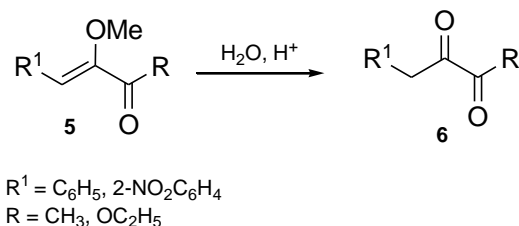
Scheme 3. Synthesis of α-diketones or esters of α-ketoacids by hydrolysis of β-aryl-α-methoxy-α,β-unsaturated ketones and esters.

The present work is aimed at the development of methods for the synthesis 2-alkoxy- and 2-alkylthio-3-aryl(hetaryl)propenals by the cross-aldol condensation of aromatic or heteroaromatic aldehydes with alkoxyacetic or butylthioacetic aldehydes. Also, we are attempting here to determine the direction of polarization of the C=C bond in these unstudied hetero acryl systems.

Results and Discussion

To find the best experimental conditions, we initially studied the pair benzaldehyde **7a** – ethoxyacetaldehyde **8a**. The reaction conditions and the product yields are given in Table 1.
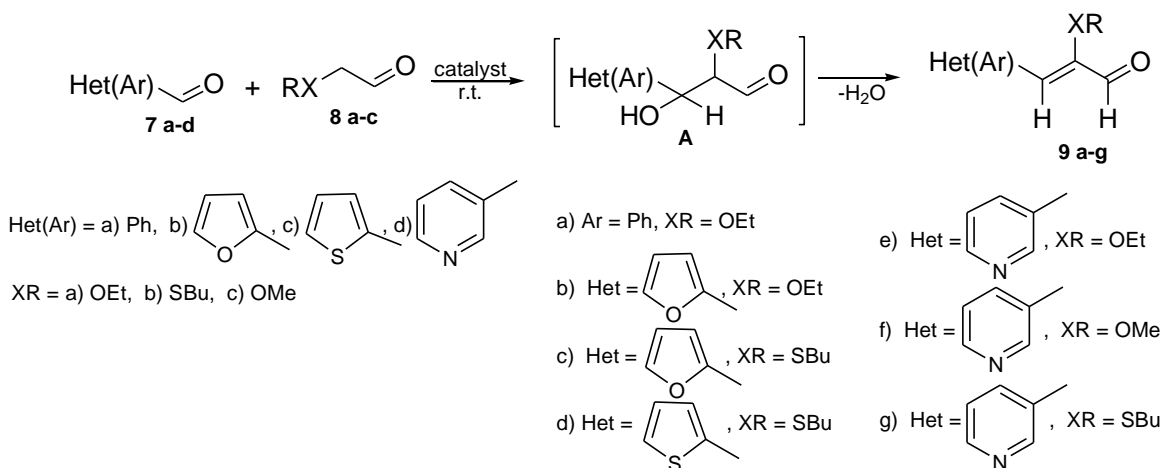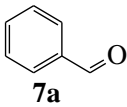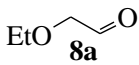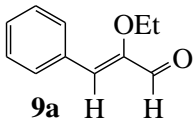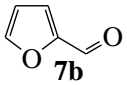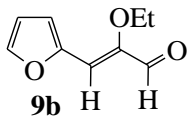

Scheme 4. Synthesis of 2-alkoxy- and 2-alkylthio-3-aryl(hetaryl)propenals by reaction of aldol condensation.
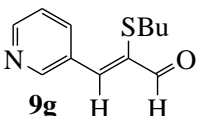
As seen from Table 1, in this case (entry 1), the most widely used conditions for condensation of benzaldehyde with alkanals, solid NaOH – benzene – TEBA (triethylbenzylammonium chloride),[15a] turns out to be of low efficacy. The reaction proceeds slowly and the yield of 3-phenyl-2-ethoxypropenal **9a** is only 13% (^{1}H NMR). The best results have been obtained in a heterogenous system solid NaOH – DMF, where the content of solid base can be varied from 13 to 100 mol % and higher (entry 2, 3). The yield reaches 97% (^{1}H NMR data) and 84% after isolation by column chromatography on silica gel.
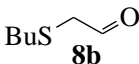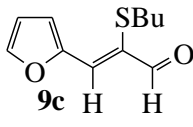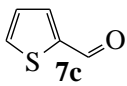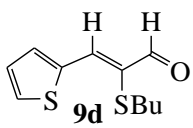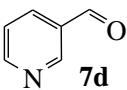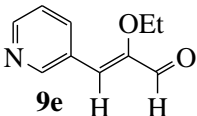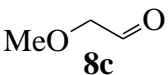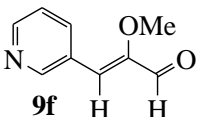
The reactions of furfural **7b** and thiophen-2-aldehyde **7c** with ethoxy- and butylthioacetaldehydes **8a-b** (entry 4, 6) have been carried out using the protocol of aldol condensation. Under these conditions, the reaction proceeds in 2 h to give the enals in 70% yield. When the duration of the reaction of furfural with ethoxyacetaldehyde is increased to 12 h, the yield of aldehyde **9b** reaches 80% (entry 5). According to the GC-MS data, in a similar experiment with butylthioacetaldehyde (entry 6), 2,4-dibutylthio-2-butenal (up to 10%) is observed (*cf.* ref. 5).

Table 1. The conditions of the condensation reactions and enal **9** yields

Entry	Reagents		Product	Reaction conditions			Yield[a] %
	7	**8**		Catalyst	Solvent	Reaction time (h)	
1	7a	EtO 8a	9a H H	NaOH-TEBA	C$_6$H$_6$	5	13
2	**7a**	**8a**	**9a**	NaOH[b]	DMF	24	97
3	**7a**	**8a**	**9a**	NaOH[c]	DMF	24	97(84)
4	7b	**8a**	9b H H	NaOH	DMF	2	71
5	**7b**	**8a**	**9b**	NaOH	DMF	12	80(61)
6	**7b**	BuS 8b	9c H H	NaOH	DMF	2	69(57)
7	7c	**8b**	9d SBu	NaOH	DMF	2	31(28)

Table 1. (continued)

Entry	Reagents		Product	Reaction conditions			Yield[a]
	7	**8**		Catalyst	Solvent	Reaction time (h)	%
8	**7d**	**8a**	**9e**	NaOH[d]	DMF	6	92(70)
9	**7d**	**8c**	**9f**	NaOH[d]	CH$_3$CN	12	69(59)
10	**7d**	**8b**	**9g**	NaOH[d]-TEBA	C$_6$H$_6$	24	98(72)
11	**7d**	**8b**	**9g**	NaOH[b]	DMF	24	67

[a] According to ^{1}H NMR data; isolated product given in parenthesis; [b] 13 mol%; [c] 130 mol%; [d] 190-200 mol%.

Thiophen-2-carbaldehyde **7c** reacts with butylthioacetaldehyde (entry 7) significantly slower: in 2 h the yield of 2-butylthio-3-thienylpropenal **9d** is only 27-31% (^{1}H NMR data). In this case, aliphatic aldehyde **8b** disappears completely from the reaction mixture, while heteroaromatic component is retained in substantial amounts. This fact as well as the increase of butylthiogroup integrals in the ^{1}H NMR spectra evidences the presence of self-condensation reactions and/or decomposition of butylthioacetaldehyde giving BuSSBu. According to GC-MS data, the content of 2,4-dibutylthio-2-butenal in the reaction mixture is about 5 mass%.

The application of the above procedures to pyridine-3-carbaldehyde **7d** proved to be fruitful. Its interaction with aldehydes **8a,b,c** leads to the target products **9e,f,g** in 70-98% yields (^{1}H NMR data) (entries 8-11). With aldehyde **7d**, the system NaOH – benzene – TEBA also works well. In this series of experiments, it was reasonable to increase the content of NaOH in the reaction mixture up to 190-200%. This concentration did not cause the side reactions: the content of 2,4-dibutylthio-2-butenal in the mixture does not exceed 6%.

Stereochemical assignment of the compounds **9** prepared at room temperature has been made using 2D-experiments HSQC, HMBC and NOESY. All the compounds are pure (*Z*)-isomers. However, the GC-MC analysis of the condensation products **9** have shown that in most cases two isomers with equal molecular weight but different fragmentation character are observed in the ratios from 5:1 (for **9c**) to 20:1 (**9f** and **9g**). Obviously, they are formed owing to the strong thermal effect in evaporator and in chromatography column (250, 280 °C). For propenal **9a** four isomers in the ratio 16 : 2 : 1 : 1 have been found. The presence of minor compounds is likely attributed to the availability of *s-cis* and *s-trans*-isomers.

The determination of the C=C bond polarization is of special importance, because it enables to predict the areas of application of the synthesized alkenals **9**. Previously, it has been shown that in 2-alkoxypropenals the competitive +M effect of the RO-group is predominant; the first step of the acidic hydrolysis being electrophilic addition of water according to Markovnikov.[17] In 3-aryl- and 3-hetarylpropenals **9**, the combined electron-withdrawing effect of the carbonyl moiety and the substituent at the position 2 would induce long conjugated system. The position 3 in this case would become highly electrophilic center allowing an easy addition of nucleophiles (in particular, water) to this center despite of steric effects of the substituents at C-3. The hydrolysis of 2-ethoxy-3-phenylpropenal **9a** in acidic medium (60 °C 1-1.5 h) results in the appearance of PhCHO **7b** which concentration increases in time (^{1}H NMR data). This fact can be explained by the initial attack of ⁻OH ion to the β-position of the double bond to afford intermediate **A** (Scheme 4) which further undergoes the retro-aldol decomposition.

Such a transformation was observed when we tried to prepare hydrazone of 2-methoxy-3-pyridyl propenal **9f**. The interaction of pure enal **9f** with 2,4-dinitrophenylhydrazine in acidic aqueous medium (pH 3, rt, 24 h) furnished 2,4-dinitrophenylhydrazone of pyridine-3-carbaldehyde **10** in 65% yield (Scheme 5). The structure of the synthesized hydrazone has been proved both by the comparison of its ^{1}H and ^{13}C NMR spectra with the spectra of reference sample and 2D-experiments HSQC and COSY.

To continue the study of aldehyde **9** properties, we have carried out the reaction of 2-butylthio-3-furylpropenal **9c** with thiosemicarbazide. Heating the reactants in acidic aqueous ethanol solution (40 °C, 20 min) affords the corresponding thiosemicarbazone **11** (Scheme 5). This reaction shows that the above hydrolytic cleavage of the C=C bond in acidic medium is not inherent for all enals **9**. Probably, 2-alkylthiosubstituted enals **9** are the exceptions. Earlier, such a resistance to the hydrolysis of alkylthiovinyl group has been strongly supported for 3-unsubstituted 2-alkylthiopropenals.[19] But this resistance is not observed in the case of substitution of carbonyl group for the acetal moiety, *i.e.* when π,π-conjugation typical for acrylic system disappears from the molecule structure.
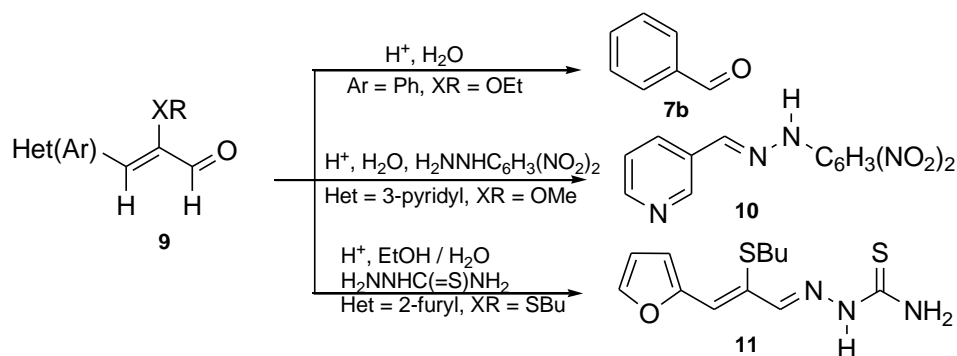
Scheme 5. Hydrolysis of some 2-functionalized 3-(hetero)aromatic propenals.

Conclusion

We have found the conditions for the reaction of aryl- or hetarylaldehydes with alkoxy- or butylthioacetaldehydes in different solvents where the main pathway is the cross-aldol condensation. These conditions allow (*Z*)-2-alkoxy- or (*Z*)-2-butylthio-3-aryl(hetaryl)propenals to be synthesized stereoselectively in moderate or high yields. The direction of hydrolytic decomposition of the propenals molecule due to the presence of combined conjugated system of aliphatic chain and heterocycles has been determined using several examples. Further investigations would reveal the scope of this conjugation effect on the reactivity of the molecules **9** in case of introduction of electron-withdrawing substitutents (NO_2, COOH) into the heteroaromatic ring or at a change of the carbonyl moiety with a less electron-withdrawing functional group (acetal, imine). This may allow the preparation of several useful synthetic precursors with potential to open an approach to new biologically active compounds.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 and AV-400 spectrometers (400.13 and 100.61 MHz, accordingly), using $CDCl_3$ as a solvent, and HMDS as an internal standard. Nuclear Overhauser effect (NOESY), homonuclear ($^1H/^1H$) correlation spectroscopy (COSY) and inverse gradient heteronuclear ($^1H/^{13}C$) 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). Commercially available benzaldehyde was treated with soda solutions to remove benzoic acid, dried over $MgSO_4$ and distilled off.

General procedure for the synthesis of enals 9a-d
The (hetero)aromatic aldehyde **7** (10 mmol) was added at once to stirred mixture of NaOH (0.1 g) in DMF (30 ml) at room temperature. A solution of alkylthio- or aqueous azeotrope of alkoxyacetaldehyde **8** (12 mmol) in DMF (5 ml) was added slowly dropwise and stirring continued for 2-24 h at room temperature until the reaction was completed (^1H NMR monitoring). The reaction mixture was diluted with water and extracted with benzene. Organic extract was washed with water 5 times (to remove DMF) and dried over $MgSO_4$. After removal of benzene in vacuum, the product was isolated by column chromatography.

(Z)-2-Ethoxy-3-phenylpropenal 9a. Yield is up to 2.77g (84%) after silica gel chromatography using hexane / ether (2 : 1). Clear liquid. ^{1}H NMR δ 1.36 (t, J = 7.0 Hz, 3H, CH$_3$), 4.25 (q, J = 7.0 Hz, 2H, CH$_2$), 6.55 (s, 1H, =CH), 7.36 (m, 3H, m-, p-H), 7.85 (d, J = 7.5 Hz, 2H, o-H), 9.34 (s, 1H, CHO). ^{13}C NMR δ 15.83 (CH$_3$), 29.74 (CH$_2$), 67.10 (=CH), 128.71(C$_{meta}$), 129.29 (C$_{para}$), 130.25 (C$_{ortho}$), 134.42 (C$_{ipso}$), 153.36 (=C-O), 189.85 (CHO). GC-MS analysis showed 4 isomers with molecular weight 176, two pairs of which have similar fragmentation character. For the pair of isomers with retention time 8.68 and 8.92 min, their ratio in the reaction mixture equals to 16:1. GC − MS: m/z (%) = 176 (41) [M$^{+\cdot}$], 147 (25), 132 (57), 119 (39), 104 (7), 91(100). For other pair of isomers with retention time 8.77 and 8.81min, the ratio is 2:1. GC-MS: m/z (%) = 176 (3) [M$^{+\cdot}$], 165 (3), 147 (2.7), 132 (3.8), 119 (16.9), 107 (26), 91 (51.5), 88 (100). IR (film): 3441, 3395, 3028, 2857, 2737, 1686 (C=O), 1622 (C=C), 1597, 1585, 1451, 1414, 1374, 1348, 1204, 1181, 1040, 827, 783, 692 cm^{-1}. Anal. Calcd for C$_{11}$H$_{12}$O$_2$: C, 75.00; H, 6.82. Found: C, 74.64; H, 6.35.

(Z)-2-Ethoxy-3-(2-furyl)propenal 9b. Yield 3.1g (61%) after silica gel chromatography using hexane / ether 3 : 1. Clear dark-orange liquid. ^{1}H NMR δ 1.34 (t, J = 7.0 Hz, 3H, CH$_3$), 4.32 (q, J = 7.0 Hz, 2H, CH$_2$), 6.52 (dd, J = 3.3 Hz, J = 1.2 Hz, 1H, H-4), 6.56 (s,1H, =CH), 7.12 (d, J = 3.3 Hz, 1H, H-3), 7.53 (d, J = 1.1 Hz, 1H, H-5), 9.24 (s, 1H, CHO). ^{13}C NMR δ 15.92 (CH$_3$), 67.02 (CH$_2$), 112.82 (C4), 115.35 (C3), 122.06 (=CH), 144.31 (C5), 149.76 (C2), 150.74 (=C-OCH$_2$), 187.74 (CHO). GC-MS analysis showed that the product contains two isomers with molecular weight 166 and retention time 7.65 and 8.02 min. For the first isomer: m/z (%) = 166 (79.0) [M$^{+\cdot}$], 138 (26) [M – CH$_2$CH$_2$], 122 (72), 110 (35), 81 (100). For the other isomer: m/z (%) = 166 (48) [M$^{+\cdot}$], 138 (21) [M – CH$_2$CH$_2$], 122 (45), 110 (29), 81 (100). IR (film): 3444, 2981, 2845, 1679 (C=O), 1619 (C=C), 1561, 1474, 1417, 1374, 1345, 1230, 1136, 1108, 1083, 1042, 1017, 826 cm^{-1}. Anal. Calcd for C$_9$H$_{10}$O$_3$: C, 65.06; H, 6.02. Found: C, 64.94; H, 6.03.

(Z)-2-Butylthio-3-(2-furyl)propenal 9c. Yield 0.5g (57%) after silica gel chromatography using hexane / ether 3 : 1. Clear dark-orange liquid. ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H, CH$_3$), 1.37 (m, 2H, CH$_2$), 1.42 (m, 2H, CH$_2$), 3.02 (t, J = 7.4 Hz, 2H, SCH$_2$), 6.60 (dd, J = 3.4 Hz, J = 1.2 Hz, 1H, H-4), 7.44 (s,1H, =CH), 7.51 (d, J = 3.4 Hz, 1H, H-3), 7.62 (d, J = 1.2 Hz, 1H, H-5), 9.49 (s, 1H, CHO). ^{13}C NMR δ 13.50 (CH$_3$), 21.66 (CH$_2$), 31.67 (CH$_2$), 32.28 (CH$_2$S), 118.18 (C4), 132.26 (=C-S), 137.59 (=CH), 145.38 (C3), 150.78 (C2), 154.44 (C5), 190.22 (CHO). GC-MS analysis showed two isomers in 5.4:1 ration with retention time 10.07 and 10.32 min. First isomer: m/z (%) = 210 (100) [M$^{+\cdot}$], 181 (10), [M – CHO], 177 (9), 163 (12), 154 (23), 125 (37), 97 (48). Second isomer: m/z (%) = 210 (100) [M$^{+\cdot}$], 181 (10) [M-CHO], 177 (10), 167 (60), 154 (28), 125 (50), 97 (70). IR (film): 3424, 3353, 2959, 2931, 2872, 1685 (C=O), 1586 (C=C), 1467, 1199, 1116, 1021, 941, 885, 752 cm^{-1}. Anal. Calcd for C$_{11}$H$_{14}$ SO$_2$: C, 62.86; H, 6.66; S, 15.24%. Found: C, 63.30; H, 6.80; S, 15.34.

(Z)-2-Butylthio-3-(2-thienyl)propenal 9d. Yield 1.12g (28%) after silica gel chromatography using hexane / ether 2 : 1. Clear dark-orange liquid. ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H, CH$_3$), 1.42 (m, 2H, CH$_2$), 1.52 (m, 2H, CH$_2$), 2.95 (t, J = 7.2 Hz, 2H, SCH$_2$), 7.12 (dd, J = 4.5 Hz, J = 2.7 Hz, 1H, H-4), 7.51 (d, J = 2.7 Hz, 1H, H-5), 7.61 (d, J = 4.5 Hz, 1H, H-3), 7.80 (s, 1H, =CH),

9.53 (s, 1H, CHO). ^{13}C NMR δ 13.88 (CH$_3$), 22.06 (CH$_2$), 32.40 (CH$_2$), 32.89 (CH$_2$S), 127.20 (C4), 132.58 (=C-S), 133.20 (C3), 135.51 (C5), 138.78 (C2), 145.00 (=CH), 190.14(CHO). GC-MS: m/z (%) = 226 (78) [M$^+$], 197 (4) [M – CHO], 183 (9), 169 (30), 153 (34), 141 (48), 122 (6), 110 (22), 97 (100). IR (film): 3448, 3346, 2958, 2929, 2871, 1682 (C=O), 1576 (C=C), 1464, 1415, 1246, 1115, 858, 716 cm^{-1}. Anal. Calcd for. C$_{11}$H$_{14}$S$_2$O: C, 58.40; H, 6.19; S, 28.32. Found: C, 58.60; H, 6.20; S, 27.93.

(Z)-2-Ethoxy-3-(3-pyridyl)propenal 9e. A solution of aqueous azeotrope of ethoxyacetaldehyde (1.12 ml, 64 mmol) in DMF (30 ml) was slowly added dropwise to a mixture of NaOH (0.53g), DMF (100 ml) and pyridine-3-carbaldehyde (0.6787g, 63 mmol). The reaction mixture was allowed to stand for one day, the water (100 ml) was added and the mixture was extracted with benzene. The extracts were washed with water and dried over MgSO$_4$. After removal of benzene in vacuum, the product was isolated on chromatographic column (eluent hexane:ether 1:6). The yield **9e** 0.78g (70%). ^{1}H NMR δ 1.36 (t, *J* = 6.8 Hz, 3H, CH$_3$), 4.33 (q, *J* = 6.8 Hz, 2H, CH$_2$), 6.52 (s, 1H, =CH), 7.33 (dd, *J* = 7.0 Hz, *J* = 4.0 Hz,1H, H-5), 8.26 (d, *J* = 7.0 Hz, 1H, H-4), 8.55 (d, *J* = 4.0 Hz, 1H, H-6), 8.92 (s, 1H, H-2), 9.39 (s, 1H, CHO). ^{13}C NMR δ 15.56 (CH$_3$), 66.95 (CH$_2$), 123.35 (=CH), 129.07 (C5), 129.46 (C3), 136.18 (C4), 149.77 (C2), 150.65 (C6), 154.18 (=C-O), 188.86 (CHO). GC-MS: m/z (%) = 177 (51.9) [M$^+$], 148 (35) [M$^+$– CHO], 133 (75), 120 (100). Anal. Calcd for C$_{10}$H$_{11}$NO$_2$ (%): C, 67.79; H, 6.21; N, 7.90. Found: C, 67.44; H, 6.00; N, 7.70.

(Z)-2-Methoxy-3-(3-pyridyl)propenal 9f. A solution of aqueous azeotrope of methoxyacetaldehyde (0.5 ml, 42 mmol) in acetonitrile (10 ml) was slowly added dropwise to a mixture of NaOH (0.425g), acetonitrile (50 ml) and pyridine-3-carbaldehyde (0.4525g, 42 mmol). The reaction mixture was allowed to stand for one day at room temperature, the solvent was removed and the product was isolated on chromatographic column (eluent hexane:ether 1:4). The yield of **9f** was 0.4g (59%). ^{1}H NMR δ 4.01 (s, 3H, OCH$_3$), 6.45 (s, 1H, =CH), 7.42 (dd, 1H, *J* = 8.0 Hz, *J* = 4.6 Hz, H-5), 8.25 (d, 1H, *J* = 8.0 Hz, H-4), 8.53 (d, 1H, *J* = 4.6 Hz, H-6), 8.89 (s, 1H, H-2), 9.41 (s, 1H, CHO). ^{13}C NMR δ 58.59 (CH$_3$), 123.71 (C5), 129.29 (=CH), 129.54 (C3), 136.75(C4), 149.82 (C6), 150.35 (C2), 154.68 (=C-OMe), 189.46 (CHO). For the first isomer: m/z (%) = 163 (100) [M$^+$], 134 (65) [M$^+$– CHO], 119 (74). For the other isomer GC-MS: m/z (%) = 163 (93) [M$^+$], 134 (82) [M$^+$– CHO], 119 (100). Anal. Calcd for C$_9$H$_9$NO$_2$ (%): C, 66.25; H, 5.52. Found: C, 66.21; H, 5.60.

(Z)-2-Butylthio-3-(3-pyridyl)propenal 9g. A solution of butylthioacetaldehyde (1g, 7 mmol) in benzene (15 ml) was slowly added dropwise to a mixture of benzene (150 ml), NaOH (0.58g), TEBA (0.029g) and pyridine-3-carbaldehyde (0.75g, 7 mmol) under stirring. The reaction mixture was allowed to stand for one day at room temperature, the water (30 ml) was added, organic layer was removed and dried over MgSO$_4$. After removal of benzene in vacuum, the compound **9g** was isolated by column chromatography (eluent hexane:ether 7:3). The yield was 1.1g (72%). ^{1}H NMR δ 0.84 (t, 3H, *J* = 7.4 Hz, CH$_3$), 1.33 (m, 2H, CH$_2$), 1.47 (m, 2H, CH$_2$), 2.97 (t, *J* = 7.4 Hz, 2H,SCH$_2$), 7.40 (dd, *J* = 8.0 Hz, 1H, *J* = 4.9 Hz, H-5), 7.56 (s, 1H, =CH), 8.45 (d, *J* = 8.1 Hz, 1H, H-4), 8.61 (d, *J* = 4.7 Hz, 1H, H-6), 8.96 (s, 1H, H-2), 9.61 (s, 1H,

CHO). ^{13}C NMR δ 13.83 (CH$_3$), 21.96 (CH$_2$), 32.42 (overlapping of chemical shifts SCH$_2$- and CH$_2$- groups), 123.59 (=CH), 130.63 (C3), 137.59 (C5), 138.94 (=C-S), 147.49 (C4), 150.99 (C2), 152.35 (C6), 191.30 (CHO). GC-MS analysis showed two isomers with molecular weight 221 and retention time 11.29 and 11.45 min. The isomers have the same fragmentation. GC-MS: m/z (%) = 221 (53) [M$^+$], 188 (27), 174 (10), 164 (58.6), 148 (15), 136(100). Anal. Calcd for C$_{12}$H$_{15}$NOS (%): C, 65.15; H, 6.78; N, 6.33; S 14.47. Found: C, 65.40; H, 6.91; N, 6.13; S, 14.86.

2,4-Dinitrophenylhydrazone of pyridine-3-carbaldehyde 10 from aldehyde 9f. To a mixture of pyridine-3-carbaldehyde (0.37 g, 0.0021 mol), water (3 ml) and DMF (10 ml) was added slowly dropwise concentrated HCl (up to pH=3). In 10 min alcohol solution of 2,4-DNPH (2,4-dinitrophenylhydrazine) (0.415 g, 0.0021 mol) was added to the reaction mixture. The compound **10** (0.39 g, 65%) precipitated immediately. After re-crystallization from ethanol mp 253.5 ℃. Sample prepared from authentic pyridine-3-carbaldehyde and 2,4-DNPH had mp 253.5 ℃. The mixed sample had no melting point depression as compared to the reference sample. Structure of the hydrazone was proved by the data of ^{1}H and ^{13}C NMR spectroscopy and 2D-experiments HSQC and COSY. The spectra of hydrazone **10** correspond to the spectra of the reference sample. ^{1}H NMR (CDCl$_3$ + 3 drops CF$_3$COOH) δ 8.06 (dd, J = 8.2 Hz, 1H, J = 5.5 Hz, H-5 Pyr), 8.13 (d, J = 9.4 Hz, 1H, H-6 Ph), 8.31 (s, 1H, =CH), 8.45 (dd, J = 9.4 Hz, 1H, J = 5.5 Hz, H-5 Ph), 8.79 (d, J = 8.2 Hz, 1H, H-2 Pyr), 9.01 (d, J = 5.5 Hz, 1H, H-6 Pyr), 9.18 (d, J = 2.4 Hz, 1H, H-3 Ph), 9.53 (s, 1H, H-2 Pyr). ^{13}C NMR (CDCl$_3$ + 3 drops CF$_3$COOH) δ 117.07 (C6 Ph), 123.34 (C3 Ph), 127.59 (C5 Pyr), 130.59 (C5 Ph), 131.12 (C1 Ph), 134.60 (C3 Pyr), 138.25 (HC=N), 140.27 (C2 Ph), 140.96 (C2 Pyr), 141.89 (C6 Pyr), 142.52 (C4 Pyr), 143.77 (C4 Ph). IR (KBr): 3448, 3297, 1620, 1584, 1515, 1327, 1314, 1276, 1234, 1124 cm^{-1}.

Thiosemicarbazone of 2-butylthio-3-(3-furyl)propenal 11. To a heated (40 ℃) ethanol / water (2:1) solution of thiosemicarbazine (0.91g, 10 mmol) was added under stirring aldehyde **9c** (2.1g, 10 mmol) and two drops of concentrated hydrochloric acid. The heating was continued for 20 min. The cooling of the solution gave 1.12g (40%) of the compound **11**. A sample was recrystallized from ethanol mp 117-118 ℃. ^{1}H NMR (DMSO-d$_6$) δ 0.88 (t, J = 7.2 Hz, 3H, CH$_3$), 1.42 (m, 2H, SCH$_2$CH$_2$C<u>H</u>$_2$), 1.53 (m, 2H, SCH$_2$C<u>H</u>$_2$), 2.83 (t, J = 7.4 Hz, 2H, SCH$_2$), 6.61 (m, 4H, H-3 and =CH and NH$_2$), 7.19 (dd, J = 3.4 Hz, J = 1.2 Hz, 1H, H-4), 7.74 (d, J = 1.2 Hz, 1H, H-5), 8.74 (s, 1H, N=CH). ^{13}C NMR δ 13.57 (CH$_3$), 21.51 (CH$_2$), 30.11 (CH$_2$), 30.14 (SCH$_2$), 112.39 (C3), 118.59 (=CH), 125.45 (C4), 129.97 (=C-S), 140.74 (N=CH), 144.04 (C5), 151.19 (C2), 178.07 (C=S). IR (KBr): 3395, 3360, 3230, 3130, 2935, 1595(C=N), 1513 (C=C) cm^{-1}. Anal. Calcd for C$_{12}$H$_{17}$N$_3$OS$_2$: C, 50.88; H, 6.00; S, 22.61; N, 14.84. Found: C, 50.90; H, 6.37; S, 22.24; N, 14.71.

Acknowledgment

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