Improved approaches in the synthesis of new 2-(1, 3-thiazolidin-2*Z*-ylidene)acetophenones

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday
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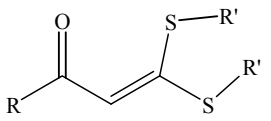
Abstract
Phenyl isothiocyanate reacts stereoselectively with several acetophenones in basic conditions to give after alkylation with dibromoethane, the corresponding new 2-(1,3-thiazolidin-2*Z*-yliden) *p*-R-acetophenones (**1b-f**). All compounds were characterized by conventional spectroscopic techniques and in the case of **1a** the structure was fully established by X ray diffraction analysis.

Keywords: Heterocyclization, thiazolidine derivatives, X-Ray crystallography

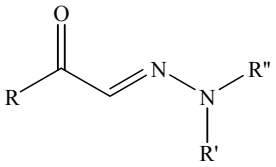
Introduction

α,β-Unsaturated carbonyl compounds are used as ligands to form either η^2 or η^4 complexes when they react with $Fe(CO)_9$.[1] Our interest in the chemistry of iron led us to synthesize new mono and dinuclear Fe(0) complexes, which have been prepared by reaction of α,β-unsaturated ketones analogues containing sulphur (**A**)[2] or nitrogen (**B**)[3] in β-position with $Fe_2(CO)_9$. In continuing with our studies, we are interested in exploring the reactivity of α,β-unsaturated ketones having both N and S atoms in β-position such as an α-oxo ketenes N,S-acetals (**1**).



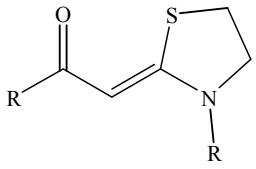
R= Alkyl, Aryl, Aryl-CH=CH
R"=H,Alkyl

A



R= Alkyl, Aryl, Aryl-CH=CH
R"=H,Alkyl

B



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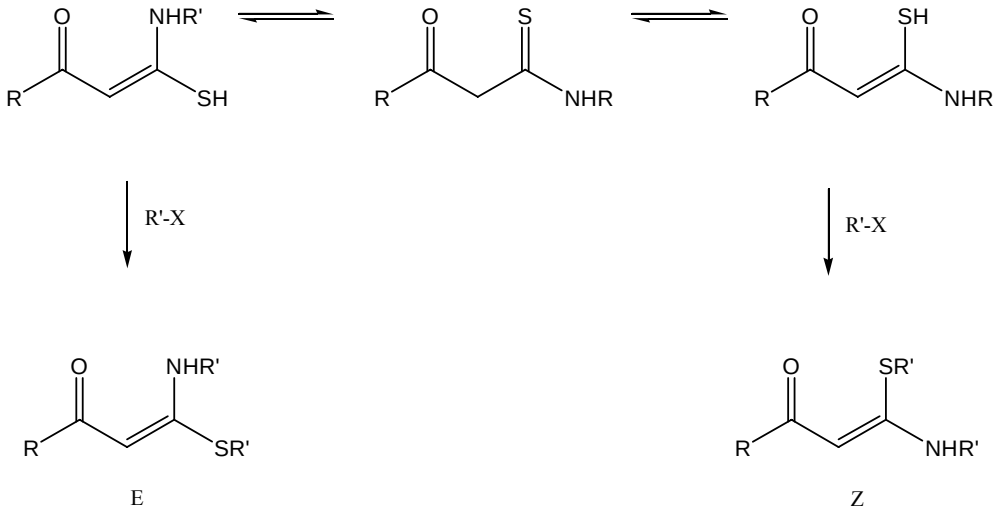
Gompper and co-workers[4] reported the synthesis of α-oxo ketene N,S-acetals from the addition of amines to ketene-dithioacetals with high yields, however this method involves a multi-step synthesis and in several cases the α-oxo ketene N,N-acetal is an important by-product.[5] This procedure was used by other research groups to obtain several heterocyclic compounds.[6] Another approach to obtain the α-oxo ketene N,S-acetals is by alkylation of the corresponding thioamide analogue. These exist as two tautomeric forms in solution, and after alkylation yield a mixture of *E*/*Z* isomers (Scheme 1).[6a]

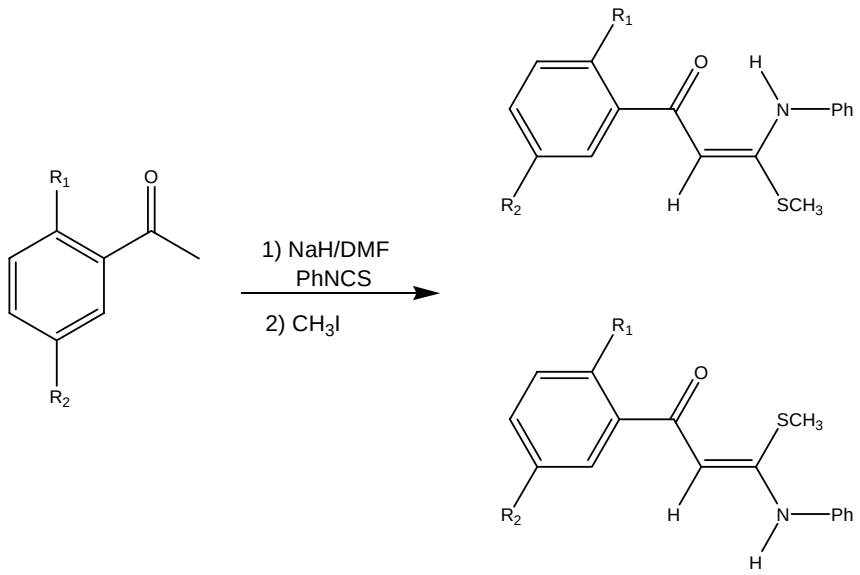


E Z

Scheme 1

In this way, alkylation reactions with 1,2-, 1,3-, and 1,4-alkyldihalides have been carried out affording thiazole, thiazine and thiazepine derivatives, respectively. Sometimes a carbonyl group protecting reaction is required as the first step, and to carry out the heterocyclization

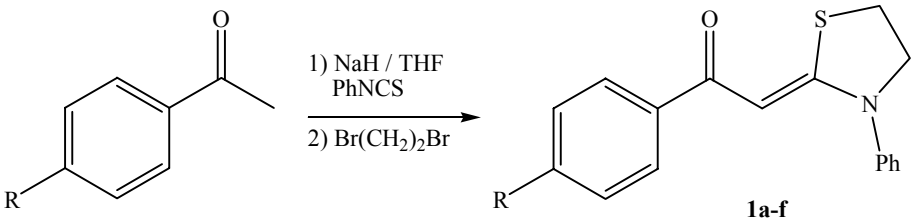
reaction phase transfer catalysis is involved.[7] A general experimental methodology for heterocyclization of α-oxo ketene thioamides is characterized firstly by the synthesis and isolation of the thioamide compound. Thus, this synthon is then treated with a dihalide to form the corresponding heterocyclic compound. Rudorf and co-workers[8] have used this methodology to prepare 1-benzoyl-2-anilino-2-methylthioethene from the reaction of an acetophenone enolate with an isothiocyanate, followed by an S-alkylation reaction (Scheme 2) giving the *E*/*Z* mixture.



Scheme 2

Results and Discussion

In this paper we report the stereoselective one-pot synthesis of several 2-(1,3-thiazolidin-2*Z*-yliden)acetophenones. The title compounds were prepared as shown in Scheme 3, using a modification to the Rudorf's methodology,[8] which involves carrying out the nucleophilic addition to an acetophenone enolate over phenyl isothiocynanate (without isolating the corresponding N-phenyl thioamide) followed by the addition of 1,2-dibromoethane *in situ*, giving after work-up only the *Z*-isomers **1a-f**.



Scheme 3

Entry	R	Yield (%)
1a	H	39
1b	F	19
1c	Cl	39
1d	Br	22
1e	NO_2	15
1f	MeO	21

The EIMS spectrum for each product showed a molecular ion consistent with the expected molecular formula. As selected data the FTIR spectra showed a narrow band at 1600 cm^{-1} assigned to the carbonyl group, a strong fine band in 1490 cm^{-1} corresponding to C=C-N vibration, in addition to the respective bands for each compound. The band intensities for the CO and C=C groups indicate that an S…O interaction through to C-C double bond was present[9] in agreement for a *Z* geometry of the double bond.

The ^{1}H NMR spectrum of **1a** showed signals corresponding to 10 benzene-ring protons (δ 7.74-7.34, m), one vinylic proton (δ 6.23, s) and four methylene protons (δ 4.03,t; and 3.21, t). The NOESY spectrum (Figure 1) suggested coupling of the vinylic hydrogen with the *ortho* hydrogens of both phenyl and N-phenyl fragments consistent with the formation of the *Z* geometric isomer. Similar results were observed for **1b-f**.

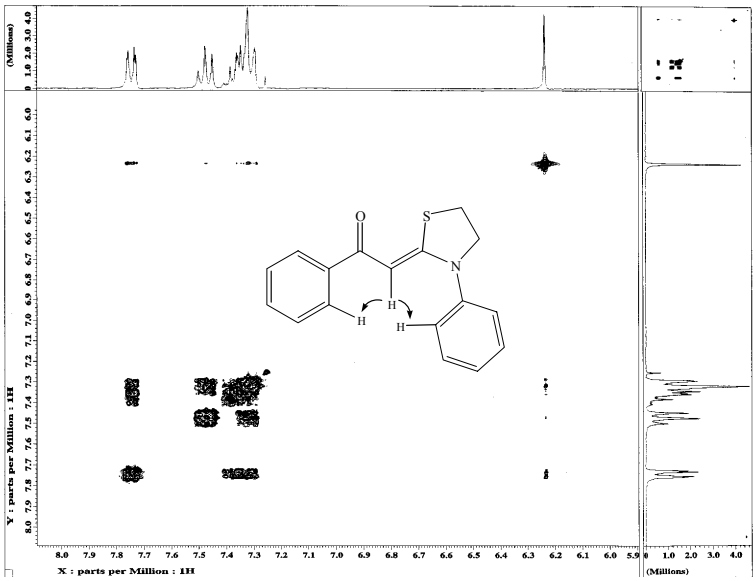


Figure 1. NMR ^{1}H (NOESY) for **1a**.

The ^{13}C NMR spectrum of **1a** exhibits two signals at δ 27.9 and 56.0, which are assigned to the C-S and C-N respectively. The C_α and C_β to the carbonyl group were observed at δ 90.4

and 166.7, and the C_{CO} at δ 186.7. For the other products (**1b-f**) similar spectroscopic data were observed.

The structural arrangement for **1a** was fully established by a single-crystal X-ray diffraction analysis.[9] The ORTEP view of this compound appears in the Figure 2 and confirms the double bond geometry assigned by NMR. This compound crystallized as two independent molecules showing the same structural arrangement. The aromatic ring bonded to ketone group is tilted 9.28º out of O=C-C=CNS plane for one conformer and 31.08º for the other. The 1,3-thiazolidine ring in both conformers adopts a half-chair conformation with C_2 axe over C10 for **C** and over C29 for **D.**

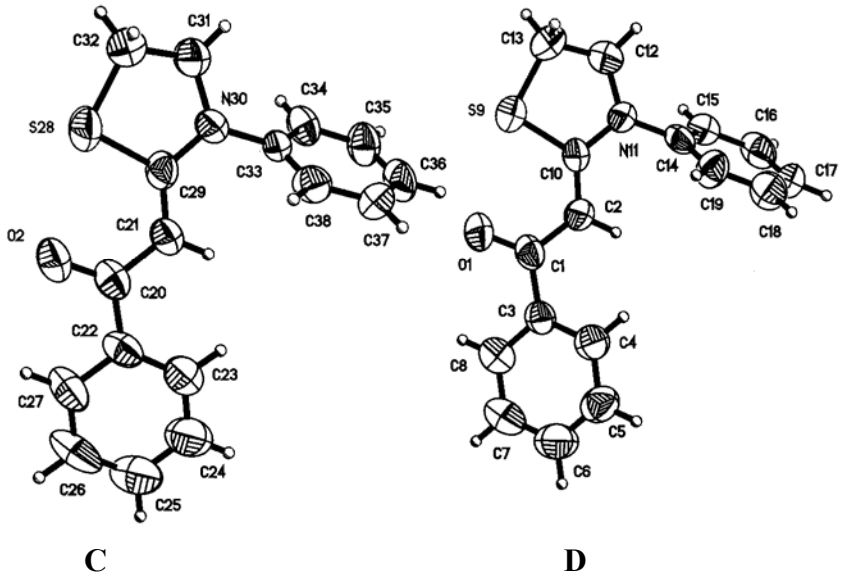


Figure 2. ORTEP drawing for **1a**. Thermal ellipsoids at 30% probability level.

The distances (O1…S9, 2.741Å and O2…S28, 2.700Å) are shorter than the ∑ of van der Walls radii, these features indicate that an interaction between the sulfur and oxygen atoms through the conjugated systems is present, in agreement with the obtained results from IR technique and, with similar systems described in the literature.[2, 10, 11] Selected bond lengths and bond angles are shown in table 2.

Table 2. Selected bond lengths (Å) and angles (º) for **1a**

O1-C1	1.24(0)	C1-C2	1.431(5)	C1-C3	1.485(5)	C2-C10	1.340(5)
S9-C10	1.740(4)	S9-C13	1.787(4)	C10-N11	1.367(4)	N11-C14	1.422(4)
N11-C12	1.444(4)	C12-C13	1.513(5)	O2-C20	1.249(4)	C20-C21	1.420(5)
C20-C22	1.486(5)	C21-C29	1.354(5)	S28-C29	1.755(4)	S28-C32	1.810(4)
C29-N30	1.357(4)	N30-C33	1.436(4)	N30-C31	1.449(4)	C31-C32	1.504(5)
O1-C1-C2	121.5(4)	O1-C1-C3	120.5(5)	C2-C1-C3	118.0(4)	C10-C2-C1	123.7(4)
C10-S9-C13	93.15(18)	C2-C10-N11	125.7(3)	C2-C10-S9	124.2(3)	N11-C10-S9	110.1(3)
C10-N11-C14	121.8(3)	C10-N11-C12	115.1(3)	C14-N11-C12	121.1(3)	N11-C12-C13	106.4(3)
C12-C13-S9	104.6(3)	C19-C14-N11	121.1(4)	C15-C14-N11	119.0(4)	O2-C20-C21	121.6(4)
O2-C20-C22	119.4(4)	C21-C20-C22	119.0(4)	C29-C21-C20	123.7(4)	C29-S28-C32	91.23(19)
C21-C29-N30	126.4(4)	C21-C29-S28	122.6(3)	N30-C29-S28	110.9(3)	C29-N30-C33	123.0(3)
C29-N30-C31	115.4(3)	C33-N30-C31	119.1(3)	N30-C31-C32	105.2(3)	C31-C32-S28	06.2(3)
C34-C33-N30	120.3(4)	C38-C33-N30	118.6(4)				

Table 3. Summary of Crystal data, data collection, and refinement details

Compound	**1a**
Formula	$C_{17}H_{15}NOS$
Molecular weigth (g mol^{-1})	281.36
Crystal size (mm)	0.194x0.186x0.070
Description	Yellow plate
Crystalline system	Triclinic
Spatial group	*P*-1
Celda parameters (Å, °)	a=9.588(1) α= 79.317)2) b=10.863(1) β=76.266(3) c=14.481(2) δ=80.481(2)
V ($Å^3$)	1428.1(3)
Z	4
$D_{calc.}$ (g cm^{-3})	1.309
No. collected reflections	20548
No. Ind. Reflections, R_{int}	6609, 0.0964
No. parameters	361
R Final, wR2[I>2σ(I)]	0.0636, 0.1215
R1, wR2 (all the dates)	0.1876, 0.1381
GOOF in F^2	1.033

Conclusions

We have found a stereoselective one-pot method for the synthesis of several 2-(1,3-thiazolidin-2*Z*-yliden)acetophenones. In all cases, a *Z* geometry according with the ^{1}H and ^{13}C NMR data were assigned and the structural arrangement for **1a** was fully established by X-Ray diffraction analysis. Reactivity studies of these compounds with $Fe_2(CO)_9$ are on development.

Experimental Section

General Procedures. FTIR spectra were recorded in solution ($CHCl_3$) using a Perkin-Elmer 283 spectrophotometer; ^{1}H, ^{13}C, NOESY and HETCOR NMR spectra were obtained on Jeol Eclipse 300 MHz instrument, using $CDCl_3$ as solvent and TMS as internal reference. The EIMS spectra were obtained from a Hewlett Packard 5953 spectrometer.
THF was distilled from sodium/benzophenone under argon immediately before used.
The reactions required inert atmosphere (nitrogen) and the reagents were used as purchased from Aldrich. Column chromatography was performed on silica gel (70-230 mesh). Melting points were determined using a Melt-Temp II capillary melting apparatus and are uncorrected.

General procedure for the syntheses of title compounds
To a stirred ice-cooled solution of NaH (8.0 mmol) in dry THF (150 mL) under nitrogen atmosphere a mixture of acetophenone (4.0 mmol) and phenyl isothiocyanate (4.0 mmol) previously dissolved in dry THF (10 mL) was added. The cooled mixture was stirred over 3 hours and 1,2-dibromoethane (4.0 mmol) was added and this mixture was cooled and stirred over 18 hours. Then, the reaction mixture was concentrated under vacuum and ethyl acetate (30 mL) was added. The organic layer was washed with water (2 X 30 mL), dried with sodium sulphate and evaporated. Finally, the residue was purified by column chromatography on silica gel and eluting with hexane/ethyl acetate in different ratios.
2-(1,3-Thiazolidin-2*Z*-ylidene)acetophenone (1a). m. p. 132 C, Selected IR Frequencies: 3010, 2867, 1603, 1571, and 1489 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (m, XH, phenyl), 7.40 (m, XH, phenyl), 6.23 (s, 1 H, C<u>H</u>CO), 4.03 (t, 2H, C<u>H</u>$_2$S), 3.21 (t, 2H, C<u>H</u>$_2$S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.7 (CO), 166.7 (CSN), 141.6 (C_{Ar}-N), 139.8 (C_{Ar}-CO), 130.9 (C9), 129.9 (C12), 128.2 (C8), 127.3 (C13), 127.3 (C7), 125.4 (C11), 90.4 (CH-CO), 56.0 (CH_2N), 28.0 (CH_2S). MS (EI) *m/z*, (%): 281 [M^+] (50), 204 [M^+- C_6H_5] (65), 77 [C_6H_5] (100).
4′-Fluoro-2-(1,3-thiazolidin-2*Z*-ylidene)acetophenone (1b). m. p. 146 C, Selected IR Frequencies: 3010, 2867, 1599, 1582, and 1489 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 9H, phenyl), 6.17 (s, 1 H, C<u>H</u>CO), 4.05 (t, 2H, C<u>H</u>$_2$S), 3.23 (t, 2H, C<u>H</u>$_2$N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1 (CO), 166.9 (CSN), 164.5 (d, *J* = 998.5 Hz, C-F), 141.5 (C_{Ar}-N), 136.0 (C_{Ar}-CO), 130.0 (C12), 129.6 (d, *J* = 36.6 Hz, C7), 127.5 (C13), 125.4 (C11), 115.1 (d, *J* = 82.4 Hz,

C8), 90.0 (CH-CO), 56.1 (CH_2N), 28.0 (CH_2S). MS (EI) *m/z*: 299 [M^+](100), 204 [M^+-C_6H_5F](40). HR-MS (FAB^+): $C_{17}H_{15}ONFS$ Exp. 300.0865, Calc: 300.0858.

4′-Chloro-2-(1,3-thiazolidin-2*Z*-ylidene)acetophenone (1c). m. p. 189 C, Selected IR Frequencies: 3009, 2875, 1603, 1564, and 1485 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 and 7.27 (system AA'BB', *J* = 8.7, 4H, phenyl), 7.38 (m, 5H, phenyl), 6.16 (s, 1 H, C<u>H</u>CO), 4.06 (t, 2H, C<u>H</u>$_2$S), 3.24 (t, 2H, C<u>H</u>$_2$S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.2 (CO), 167.3 (CSN), 141.4 (C_{Ar}-N), 138.1 (C-Cl), 137.0 (C_{Ar}-CO), 130.0 (C12), 128.7 (C7), 128.4 (C8), 127.5 (C13), 125.4 (C11), 90.0 (CH-CO), 56.1 (CH_2N), 28.0 (CH_2S). MS (EI) *m/z*: 315 [M^+](100), 204 [M^+-C_6H_5Cl](80).

4′-Bromo-2-(1,3-thiazolidin-2*Z*-ylidene)acetophenone (1d). m. p. 187 C, Selected IR Frequencies: 3010, 2859, 1604, 1561, and 1499 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 and 7.45 (system AA'BB', *J* = 8.5, 4H, phenyl), 7.39 (m, 5H, phenyl), 6.14 (s, 1 H, C<u>H</u>CO), 4.10 (t, 2H, C<u>H</u>$_2$S), 3.28 (t, 2H, C<u>H</u>$_2$S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3 (CO), 167.3 (CSN), 141.4 (C_{Ar}-N), 138.1 (C_{Ar}-CO), 131.4 (C8), 130.0 (C12), 128.9 (C7), 127.5 (C13), 125.5 (C-Br), 125.4 (C11), 90.0 (CH-CO), 56.1 (CH_2N), 28.0 (CH_2S). MS (EI) *m/z*: 361 [M^+] (75), 204 [M^+-C_6H_5Br](80). HR-MS (FAB^+): $C_{17}H_{15}ONBrS$ Exp. 360.0054, Calc: 360.0058.

4′-Nitro-2-(1,3-thiazolidin-2*Z*-ylidene)acetophenone (1e). m. p. 125 C, Selected IR Frequencies: 3010, 2866, 1588, and 1500 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 and 7.85 (system AA'BB', *J* = 9, 4H, phenyl), 7.41 (m, 5H, phenyl), 6.14 (s, 1 H, C<u>H</u>CO), 4.10 (t, 2H, C<u>H</u>$_2$S), 3.28 (t, 2H, C<u>H</u>$_2$S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.8 (CO), 168.5 (CSN), 149.0 (C-NO_2), 145.1 (C_{Ar}-CO), 141 (C_{Ar}-N), 130.0 (C12), 128.1 (C7), 127.8 (C13), 125.4 (C1), 123.4 (C8), 90.2 (CH-CO), 56.3 (CH_2N), 27.9 (CH_2S). MS (EI) *m/z*: 326 [M^+](90), 309[M^+- OH](100), 279[M^+- HNO_2](40), 204 [M^+-$C_6H_5NO_2$](90).

4′-Methoxy-2-(1,3-thiazolidin-2*Z*-ylidene)acetophenone (1f). m. p. 134 C, Selected IR Frequencies: 3010, 2840, 1600, 1570, and 1488 cm $^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 and 7.84 (system AA'BB', *J* = 8.5, 4H, phenyl), 7.40 (m, 5H, phenyl), 6.23 (s, 1 H, C<u>H</u>CO), 4.02 (t, 2H, C<u>H</u>$_2$S), 3.80 (s, 3H, Me), 3.20 (t, 2H, C<u>H</u>$_2$S). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7 (CO), 166.0 (CSN), 161.9 (C_{Ar}-O), 141.8 (C_{Ar}-N), 132.4 (C_{Ar}-CO), 129.9 (C12), 129.3 (C7), 127.1 (C13), 125.4 (C11), 113.4 (C8), 90.1 (CH-CO), 55.9 (MeO), 55.4 (CH_2N), 28.0 (CH_2S). MS (EI) *m/z*: 311 [M^+] (45), 204 [M^+-$C_6H_5OCH_3$](28), 135 [M^+-$C_8H_8O_2$](100). HR-MS (FAB^+): $C_{18}H_{18}O_2NS$ Exp. 312.1055, Calc: 312.1058.

X-Ray crystal structure determinations of compound 1a

Data collection and refinement parameters are summarized in Table 3. The diffraction data for **1a** was collected on a Bruker Smart Apex CCD diffractometer with MoKα radiation, λ = 0.71063 Å. Each data set was corrected for Lorentz and polarization effects and analytical absorption corrections based on face indexed were applied. The structures were solved by direct methods[12] and each structure was refined by full-matrix least squares on F^2 using all data with the all non-hydrogen atoms assigned anisotropic displacement parameters and hydrogen atoms bound to carbon atoms inserted at calculated position with isotropic temperature factor 1.2 times

the Uiso of the parent carbon atom. The program used in the final refinements was SHELXL-97.[13] Selected bond lengths and bond angles are shown in Tables 1-2.

Supplementary data

Crystallographic data or the structural analysis has been deposited with the Cambridge Crystallographic Centre CCDC No. 275796 for compound **1a**. Copies of this information may be obtained free of charge from The Director, 12 Union Road, Cambridge, CB2 IEZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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