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Alkylation of Benzoyl and Furoylthioureas as Polydentate Systems

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Abstract—A study of the behaviour towards alkylation of a series of benzoyl and furoylthioureas with 3,3-disubstitution has been carried out using NMR determinations. X-Ray data and semiempirical theoretical calculations demonstrated that the most stable conformation for these molecules is the so-called *quasi*-**S**. Also an explanation of the high selectivity towards the S-alkylation of these systems, based on the high contribution of the sulphur atom to the HOMO in acylthioureas is given for the title compounds. Steric factors are responsible for the difference between the percentages obtained for the S-alkylated product in 1-(4-methylbenzoyl)-3,3-diethylthiourea and 1-benzoyl-3,3-dibenzylthiourea.

Introduction

The alkylation of bidentate and polydentate systems is a topic of current interest in organic synthesis from a theoretical as well as a practical point of view.[1–3] In this regard, acylthioureas are intriguing polydentate molecules endowed with three different nucleophilic centres (S, N, and O) which can react with alkylating agents in different sites. Thus, a study of the behaviour of these nucleophiles with alkylating agents opens up new perspectives to predict the formation of specific series of S-, N- and O-isomers.

In previous works[4,5] the alkylation of a series of 3,3-disubstituted benzoylthioureas has been reported and it was confirmed that alkylation leads preferentially to S-alkylated products. However the reasons for this preference for the S-alkylation was not discussed in those works. The so-called form-**W**[6] was proposed as the most stable conformation for these acylthioureas, which do not exhibit an internal hydrogen bond (Fig. 1). This has a resemblance with β-dicarbonyl non-cyclic anions, for which this form is the most stable one when dissociated.[7]

In this paper we report on the behaviour of 3,3-disubstituted benzoyl and furoylthioureas when reacted with alkylating reagents. X-Ray diffraction data and calculated energy and net charges for the HOMO of these acylthioureas reveal that the actual stable conformation for this type of anion is the so-called *quasi*-**S**, similar to the **S**-form (see Fig. 1). Data obtained by semiempirical calculations predict that the contribution to the formation of the HOMO is just that corresponding to the sulphur atom, which explains the high selectivity towards the S-alkylation of these systems. The remarkable difference between the ratios of S-alkylated product which are observed in the case of 1-(4-methylbenzoyl)-3,3-diethylthiourea and 1-benzoyl-3,3-dibenzylthiourea was proven to be mainly due to steric factors.

Results and Discussion

The thioureas studied (see Fig. 2) were synthesised by the procedure previously reported in the literature.[4] Thioureas **1** and **2** were obtained as crystalline solids in 70–98% yields (see Experimental).

The structure of the substituted thioureas prepared was confirmed by spectroscopic techniques. Thus, the ^{1}H NMR spectra of compounds **1** and **2** show the NH proton

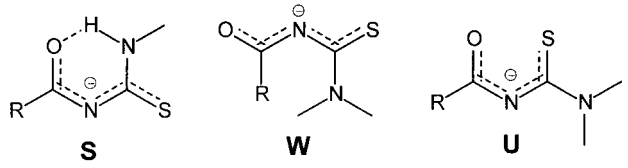

Figure 1.

Keywords: alkylation; polydentate system; thioureas; theoretical calculations.

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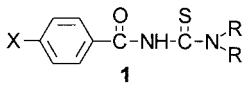
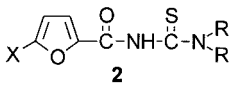


1

a, X = H; R = CH_3
b, X = H; R = C_6H_5
c, X = H; R = $CH_2C_6H_5$
d, X = $HNCOCH_3$; R = $CH_2C_6H_5$
e, X = CH_3; R = C_2H_5



2

a, X = H; R = CH_3; R' = C_6H_5
b, X = H; R = CH_3; R' = C_6H_5
c, X = H; R = R' = $CH_2C_6H_5$

Figure 2.

Table 1. Relative percentages of the S-, N-, O-alkylated isomers obtained from 3,3-disubstituted 1-(4-X-benzoyl) and 1-(5-X-furoyl) thioureas

Compound	(%) S	(%) N	(%) O
1a[a]	87	11	2
1b[a]	97	1	2
1c[b]	64	24	12
1d[b]	72	19	9
1e[b]	87	5	2
2a[b]	97	1	2
2b[b]	55	21	24
2c[b]	78	10	12

[a] Alkyl=ethyl.
[b] Alkyl=methyl.

at $\delta\sim8.5$. The ^{13}C NMR spectra show the C=S and C=O signals at $\delta\sim180$ and ~164, respectively.

Table 1 lists the results of the ethylation and the methylation carried out on thioureas **1** and **2**, respectively. As expected, the behaviour of these thioureas is quite similar; the 3,3-disubstituted thioureas can be alkylated on any of their three centres, producing three isomeric products S-, N- and O-alkylated and, in all cases, S-alkylation is predominant. This is independent of the substituents and the nature of the alkylating agent employed, an observation which is in agreement with the results previously reported.[8]

In order to explain the predominance of S-alkylation, the preferential conformation of the thiourea as well as the electrostatic factors involved in these process, were analysed. A previous paper[4] stated that of the three extreme possible conformations for the 3,3-disubstituted acylthioureas, the **W** conformation has the lowest energy because the distance between the oxygen and sulphur atoms has its maximum value. Nevertheless, it is known that for 3-mono-substituted 1-acylthioureas only the **S** conformation exists, which is stabilised because of the presence of intramolecular hydrogen bonding.[9]

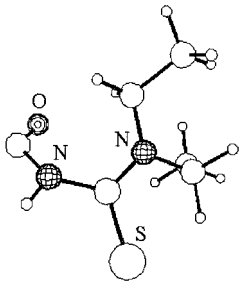


Figure 4. The thiourea in a 'quasi-**S**' conformation.

In this work the 1-(4-methylbenzoyl)-3,3-diethylthiourea (**1e**) was used as a template to determine, by means of semiempirical methods and by X-ray diffraction (see Fig. 3), the most relevant structural features for these substituted thioureas.

According to X-ray data, the acylthioureide group presents a *quasi*-**S** conformation in which the anion's charge is delocalised (see Fig. 4).

X-Ray analysis also reveals that **1e** presents a nearly planar region involving the aryl and carbonyl moieties (C4–C5–C8–O torsion angle=8.7°), thus contributing to the extension of conjugation of the molecule.

Table 2 shows selected data of bond distances, bond angles and torsion angles, obtained from X-ray diffraction studies and calculated from semiempirical methods AM1 and PM3 for 1-(4-methylbenzoyl)-3,3-diethylthiourea (**1e**).

The geometrical features predicted by AM1 and PM3 calculations and determined by X-ray diffraction listed in Table 2 showed a satisfactory correspondence of the theoretical values with the experimental values and in spite of some differences found in the torsion angles, the results confirmed that the semiempirical method AM1, as well as PM3, report a reliable geometry for the proposed systems. These data indicate that the most stable conformation for the calculated molecules is the so-called **S**. We have also determined the preferential conformation of the acylthiourea anion by semiempirical methods.

The relative stability of the three possible conformers for **1e** anion (**S**, **U** and **W**), was studied by variation of the heat of formation against the dihedral angle related to the

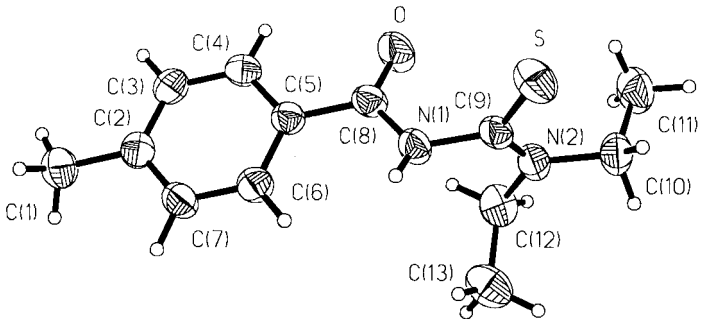


Figure 3. X-Ray structure of compound **1e** showing the numbering scheme.

Table 2. Most relevant bond distances, valence angles and dihedral angles for compound **1e** (the numbering scheme is shown in Fig. 2). Bond distances are given in Å and angles in degrees (standard deviations in parenthesis)

1e	X-Ray	AM1	PM3
Bond distances			
C5–C8	1.488(4)	1.490	1.490
C8–O	1.223(3)	1.243	1.220
C8–N1	1.349(4)	1.396	1.434
C9–N2	1.325(4)	1.373	1.378
C9–N1	1.432(3)	1.414	1.454
C9–S	1.656(3)	1.635	1.660
C10–N2	1.471(4)	1.458	1.493
C12–N2	1.471(4)	1.450	1.491
Valence angles			
C4–C5–C8	118.7(2)	117.98	119.2
C6–C5–C8	123.5(3)	122.09	121.26
O–C8–N1	120.5(3)	122.46	119.64
O–C8–C5	122.1(3)	121.44	124.17
N1–C8–C5	117.3(2)	116.09	116.15
N2–C9–N1	114.4(2)	122.42	116.88
N2–C9–S	126.4(2)	122.48	125.18
N1–C9–S	119.2(2)	115.04	117.80
N2–C10–C11	112.2(3)	114.85	112.95
N2–C12–C13	112.5(3)	115.33	112.61
C8–N1–C9	121.6(2)	128.74	124.57
C9–N2–C10	120.9(2)	118.37	119.55
C9–N2–C12	123.4(2)	125.80	125.96
C10–N2–C12	115.6(3)	115.48	114.37
Dihedral angles			
C3–C4–C5–C8	174.7(3)	179.22	179.39
C8–C5–C6–C7	−174.6(3)	−179.02	178.95
C4–C5–C8–O	−8.7(4)	−36.84	24.45
C4–C5–C8–N1	173.9(3)	142.31	−153.39
O–C8–N1–C9	5.4(4)	5.74	15.57
C5–C8–N1–C9	−177.2(2)	−173.40	−166.47
N2–C9–N1–C8	−85.9(4)	−41.57	−69.12
S–C9–N1–C8	95.8(3)	141.17	114.76
N1–C9–N2–C10	−178.8(2)	172.03	176.77
S–C9–N2–C10	−0.7(4)	−10.92	−7.43
N1–C9–N2–C12	−2.2(4)	−15.04	−7.29
S–C9–N2–C12	175.9(2)	162.01	168.5

interconversion of these conformations. Fig. 5 represents the variation of the dihedral angle that corresponds to the interconversion: **S**⇌**U** and **S**⇌**W**, respectively. In the first case (Fig. 5a), the dihedral angle S–C9–N1–C8 was rotated every 10° from −180° (**S**) to 180° (**S**), passing through 0° (**U**), the dihedral angle O–C8–N1–C9 being fixed at zero.

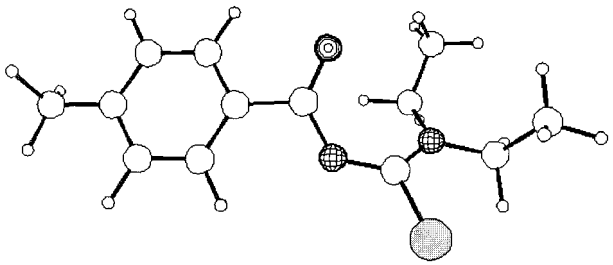


Figure 6. Semiempirical (AM1) optimised geometry for lowest energy conformer of **1e** anion.

In the second case (Fig. 5b), the dihedral angle C9–N1–C8–O was rotated every 10° from zero (**S**) to 360° (**S**) passing through 180° (**W**). The dihedral angle S–C9–N1–C8 was, in this case, fixed at 180°. These calculated data are in full agreement with those obtained for the neutral molecule, which predict the **S** conformation as the most stable one.

Fig. 6 shows the preferential conformation of the 1-(4-methylbenzoyl)-3,3-diethylthiourea anion after AM1 full optimisation geometry. It becomes evident that the predicted lower energy conformation is in agreement with that observed by X-ray diffraction, being either for the neutral thiourea or for its anion the conformation with **S** geometry. This result is in agreement with the experimental data reported by Bram.[10]

It should be noted that this geometry provides a greater access to the region of the sulphur atom compared to the O and N1 atoms, and this brings about a qualitative explanation for the higher percentage of the S-alkylated product in comparison to N- and O-alkylation.

The values of the net charge for 1-(4-methylbenzoyl)-3,3-diethylthiourea (**1e**) and its anion are shown in Table 3.

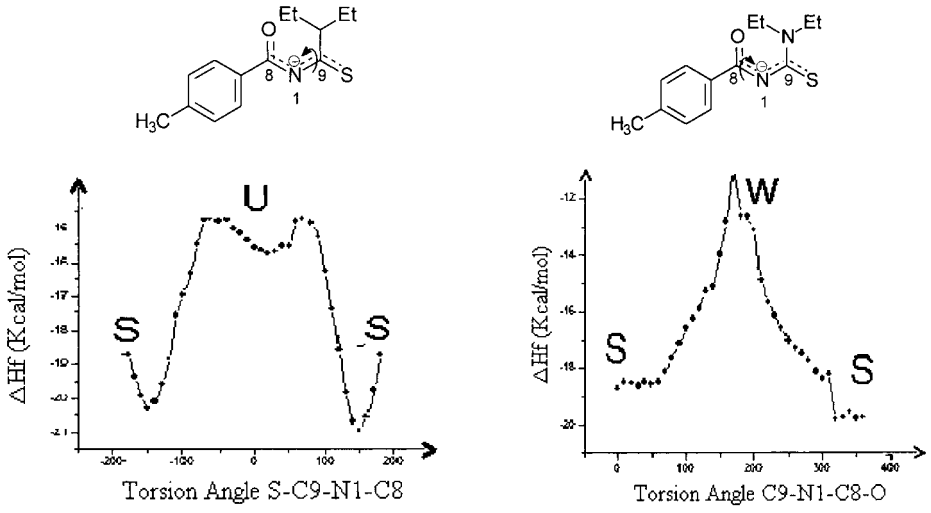


Figure 5. (a) Heat of formation vs. dihedral angle S–C9–N1–C8. (b) Heat of formation vs. dihedral angle C9–N1–C8–O.

Table 3. Net charges on S, O and N in the molecule and anion of 1-(4-methylbenzoyl)-3,3-diethylthiourea by AM1 and PM3 semiempirical methods and HF/3-21G* ab initio method

	AM1			PM3			HF/3-21G*		
	S	O	N	S	O	N	S	O	N
Molecule	−0.300	−0.342	−0.353	−0.326	−0.359	−0.041	−0.284	−0.585	−0.811
Anion	−0.539	−0.470	−0.419	−0.607	−0.446	−0.344	−0.423	−0.735	−0.884

These data were taken into account in order to evaluate the influence of the electrostatic factor in the thioureas that can also contribute to the observed preferential alkylation.

Data from Table 3 reveal that semiempirical and ab initio calculations predict the delocalisation of the negative charge over the three centres. The slightly more negative value on the sulphur atom does not explain the high alkylation ratio through this centre. In addition, atomic charges calculated by ab initio HF/3-21G* method predicts the sulphur atom to be the less negative in comparison with the O and N atoms.

Table 4 shows the contribution of the three nucleophilic centres present in the polydent anion to the HOMO of the molecule.

Table 4 reveals the preferential alkylation on the sulphur atom. The orbital coefficient calculations of the different centres show that the contribution to the formation of the HOMO is nearly exclusively from the sulphur atom. The highest occupied molecular orbital is mainly localised on this centre, while the other two atoms (O and N) have a negligible contribution to the HOMO. These findings indicate the high influence that the orbitalic component (Fukui–Khlopmann–Salem equation) has on those reactions in which the anion exhibits a remarkable nucleophilic character.

The values reported in Table 4 provide a convincing qualitative explanation based on the coefficient values of the HOMO for the total predominance of S-alkylation with respect to O- and N-alkylation.

Table 4. Calculated HOMO energy for 1-(4-methylbenzoyl)-3,3-diethylthiourea anion and contribution of the S, N and O atoms to the orbital coefficient

	AM1				PM3		
E_{HOMO}	Orbital coefficient			E_{HOMO}	Orbital coefficient		
−3.93	S	O	N	−3.93	S	O	N
	0.87	–	–		0.90	–	–

Table 5. Net charges values on S, O and N atoms in the 1-benzoyl-3,3-dibenzylthiourea anion

	AM1			PM3		
	S	O	N	S	O	N
Anion	−0.527	−0.465	−0.420	−0.637	−0.400	−0.353

These results were compared with those of the 1-benzoyl-3,3-dibenzylthiourea (**1c**) in which larger steric hindrance occurs close to the reaction centre. The comparison of the two alkylated thioureas, 1-(4-methylbenzoyl)-3,3-diethylthiourea (**1e**) and 1-benzoyl-3,3-dibenzylthiourea (**1c**), shows significant differences in the percentages of alkylation on the sulphur atom (87 and 64%, respectively, see Table 1). Again, theoretical and experimental data for the 1-(4-methylbenzoyl)-3,3-diethylthiourea were used in this analysis.

Tables 5 and 6 show the corresponding net charges data on S, O and N atoms and the calculated energy of the HOMO and orbital coefficients values, respectively, for the anion of 1-benzoyl-3,3-dibenzylthiourea using AM1 and PM3 semiempirical methods. In addition, Fig. 7 shows the most stable conformation of the 1-benzoyl-3,3-dibenzylthiourea anion after a full optimisation of its geometry.

The data from Tables 5 and 6 as well as Fig. 6 show that the anion presents a preferential **S** conformation, in spite of the large size of the two benzyl groups as substituents on N3.

When the values of the net charges (Table 5) are compared as well as the values accounting to the HOMO contribution to the donor atoms (Table 6), it becomes evident that for

Table 6. Calculated data for the energy of the HOMO of the 1-benzoyl-3,3-dibenzylthiourea anion and contribution to the orbitalic coefficient of the S, O and N atoms

	AM1				PM3		
E_{HOMO}	Orbitalic coefficient			E_{HOMO}	Orbitalic coefficient		
−4.25	S	O	N	−4.50	S	O	N
	0.86	–	–		0.84	–	–

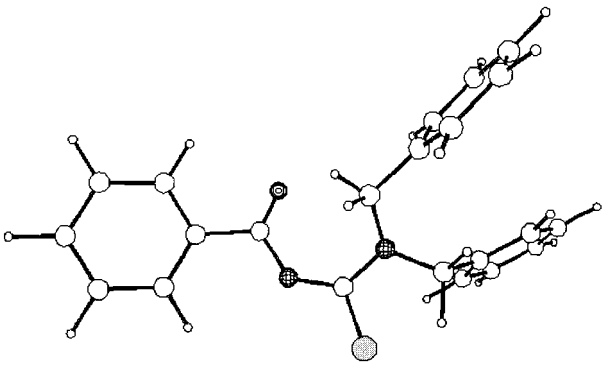


Figure 7. Semiempirical (AM1) optimised geometry for lowest energy conformer of 1-benzoyl-3,3-dibenzylthiourea anion.

both series of data, the variations from one compound to the other are not significant. Thus, this comparison makes it possible to assure that the electrostatic factors in this case are not responsible for the difference observed in the percentage of S-alkylation in both thioureas.

In summary, the experimental and theoretical data obtained in this work allow the conclusion that the steric factors are responsible for the remarkable differences found in the alkylation of thioureas.

Experimental

Melting points were determined in a capillary tube in a Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC spectrometer (250 MHz, ^{1}H and 62.0 MHz, ^{13}C) in DMSO-d_6 and $CDCl_3$. Chemical shifts are given as δ values against tetramethylsilane as the internal standard. The IR spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silicagel plates (Merck $60F_{250}$) and using benzene/methanol (9:1) as the eluent.

Semiempirical AM1[11] and PM3[12] calculations were carried out by using the mopac[13] molecular orbitals set. Previously, the molecular geometry was optimised by using Allinger's Molecular Mechanics[14] with pcmodel program.[15] Calculations were performed on a PC 486/33 computer. The ab initio calculations were carried out at the Hartree–Fock level using the 3-21G basis set (HF/3-21G). The calculation was performed using the Gaussian 94[16] program on an IBM RS/6000 workstation at the Departamento de Química Física, Universidad de Valencia.

1-Acyl-3,3-alkylthioureas (1a–e and 2a–c) were obtained by the standard procedure previously reported in the literature.[3]

1-Benzoyl-3,3-dimethylthiourea (1a). 75% yield (from acetone–H_2O), mp 175–176°C; ν_{max}/cm^{-1} 3200 (N–H), 3000 (C–H), 2910 (C–H), 1680 (C=O), 1600 (C=C), 1550 (band I, N–C=S), 1390 (band II, N–C=S), 1180 (band III, N–C=S) and 930 (band IV N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.51 (1H, s, NH), 7.85–7.55 (5H, m, Ph), 3.50 (3H, s, CH_3) and 3.28 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 180.4 (CS), 163.9 (CO), 132.9, 132.2, 128.4 (2C), 128.0 (2C) (aromatics), 43.8 (CH_3) and 42.0 (CH_3). Anal. Calcd $C_{10}H_{12}N_2OS$ (208.28): C, 57.67; H, 5.81; N, 13.45. Found: C, 57.88; H, 5.92; N, 13.60.

1-Benzoyl-3,3-diphenylthiourea (1b). 98% yield (from acetone–H_2O), mp 205–206°C; ν_{max}/cm^{-1} 3150 (N–H), 3000 (CH), 2910 (C–H), 1680 (C=O), 1610 (C=C), 1520 (band I, N–C=S), 1350 (band II, N–C=S), 1160 (band III, N–C=S) and 930 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.72 (1H, s, NH) and 7.90–7.50 (15H, m, Ph); ^{13}C NMR (DMSO-d_6) δ 179.0 (CS), 164.0 (CO), 144.7, 144.1, 133.4, 132.4, 128.9 (2C), 128.7 (2C) 128.1 (2C), 127.9 (2C), 118.3, 118.1, 116.9 (2C) and 116.1 (2C) (aromatics). Anal. Calcd $C_{20}H_{16}N_2OS$ (332.42): C, 72.26; H, 4.85; N, 8.43. Found: C, 72.41; H, 4.92; N, 8.76.

1-Benzoyl-3,3-dibenzylthiourea (1c). 81% yield (from acetone–H_2O), mp 136–138°C; ν_{max}/cm^{-1} 3330 (N–H), 3000 (C–H), 2900 (C–H), 1690 (C=O), 1583 (C=C), 1522 (band I, N–C=S), 1350 (band II, N–C=S), 1192 (band III, N–C=S) and 932 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.80 (1H, s, NH), 8.11–7.35 (15H, m, Ph), 5.32 (2H, s, CH_2) and 4.83 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 181.9 (CS), 164.0 (CO), 137.2, 136.4, 132.9, 132.2, 129.7 (2C), 129.1 (2C), 128.6 (2C), 128.4 (2C), 128.0 (2C), 127.6 (2C), 127.0, 126.8 (aromatics), 56.5 (CH_2) and 55.8 (CH_2). Anal. Calcd $C_{22}H_{20}N_2OS$ (360.47): C, 73.30; H, 5.59; N, 7.77. Found: C, 73.51; H, 5.72; N, 7.92.

1-(4′-Acetamidobenzoyl)-3,3-dibenzylthiourea (1d). 84% yield (from acetone–H_2O), mp 160–162°C; ν_{max}/cm^{-1} 3250 (N–H), 3000 (C–H), 2910 (C–H), 1680 (C=O), 1690 (C=O), 1600 (C=C), 1530 (band I, N–C=S), 1380 (band II, N–C=S), 1170 (band III, N–C=S) and 930 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.53 (1H, s, NH), 7.95–7.71 (14H, m, Ph), 7.25 (1H, s, NH), 4.82 (2H, s, CH_2), 4.62 (2H, s, CH_2) and 2.13 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 179.1 (CS), 168.5 (CO), 162.6 (CO), 143.1, 137.4, 136.6, 132.9 (2C), 132.2 (2C), 128.9, 128.4 (2C), 128.2 (2C), 128.0 (2C), 127.4 (2C), 127.1, 126.8 (aromatics) 53.6 (CH_2), 52.4 (CH_2) and 24.0 (CH_3). Anal. Calcd $C_{24}H_{23}N_3O_2S$ (417.53): C, 69.04; H, 5.55; N, 10.06. Found: C, 69.16; H, 5.25; N, 10.38.

1-(4′-Methylbenzoyl)-3,3-diethylthiourea (1e). 70% yield (from acetone–H_2O), mp 143–145°C; ν_{max}/cm^{-1} 3280 (N–H), 3040 (C–H), 2870 (C–H), 1635 (C=O), 1610 (C=C), 1515 (band I, N–C=S), 1340 (band II, N–C=S), 1140 (band III, N–C=S) and 920 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 10.41 (1H, s, NH), 7.83 (2H, d, J=8.2 Hz), 7.50 (2H, d, J=8.2 Hz), 3.95 (2H, q, CH_2CH$_3$), 3.51 (2H, q, CH_2CH$_3$), 2.37 (3H, s, CH_3), 1.25 (3H, t, CH_2CH_3) and 1.18 (3H, t, CH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 180.6 (CS), 163.8 (CO), 139.1, 130.1, 128.9 (2C), 128.1 (2C) (aromatics), 47.1 (CH_2), 46.4 (CH_2), 21.0 (CH_3), 13.3 (CH_3) and 11.1 (CH_3). Anal. Calcd $C_{13}H_{18}N_2OS$ (250.36): C, 62.37; H, 7.25; N, 11.19. Found: C, 62.48; H, 7.32; N, 11.23.

X-Ray structure analysis

Crystals of **1e** were grown by slow evaporation from acetone solution.[20]

Crystal data. $C_{13}H_{18}N_2OS$, M=394.108. Monoclinic, a=12.703(1), b=5.577(1), c=17.389(2) Å, α=90.00(0.00), β=103.93 (1), γ=90.00(0.00)°, V=1199.7 (5) Å^3 (by least-squares refinement on diffractometer angles for 40 automatically centred reflections with $3.93<\theta<69.17$, λ=0.71069 Å, T=293(2) K), space group $P2_1/c$, Z=4, D_c=1.235 g cm^{-3}, μ=0.642 mm^{-1}. A prismatic colourless crystal (0.40×0.23×0.007 mm^3) was used for the analysis. The structure was solved using direct methods shelxl 86 program.[17,18] Most of the non-hydrogen atoms were located in the E-map, and the remainder were found in a subsequent difference electron density map. They were refined on F^2 (hkl) by full-matrix least-squares, originally with isotropic

and later anisotropic temperature factors. All the H-atoms were calculated at the idealised positions based on the molecular geometry with C–H=O.96 Å, except for H1 whose coordinates were located in the electron density map. Isotropic temperature factors were set at 1.2 times Beq with respect to the corresponding atom to which they are bonded. Hydrogen atom coordinates were refined in subsequent least-square cycles. Refinement was continued until all shift error ratios were <0.1. Least-squares refinement was performed minimising the function $\sigma w=|>F_o|+|F_e|^2$, where $w=1$, in the early stages of refinement and $w=[1/\sigma^2 F=F(F_o)]$ in the final cycles. Neutral-atom scattering factors were used. All programs used are part of the shelxt-plus package.[19]

1-Furoyl-3-methyl-3-phenylthiourea (2a). 80% yield (from acetone–H_2O), mp 129–130°C; ν_{max}/cm^{-1} 3225 (N–H), 3020 (C–H), 2890 (C–H), 1695 (C=O), 1615 (C=C), 1540 (band I, N–C=S), 1400 (band II, N–C=S), 1170 (band III, N–C=S) and 920 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.61 (1H, s, NH), 7.52–7.40 (5H, m, Ph), 6.53 (1H, d, H5, J=2.0 Hz), 6.12 (1H, d, H3, J=3.1 Hz), 5.80 (1H, m, H4), 3.43 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 171.0 (CS), 160.9 (CO), 151.0 (C2), 144.5, 142.9 (C5), 129.8 (2C), 128.6 (2C), 127.1 (aromatics), 115.0 (C3), 111.4 (C4) and 45.3 (CH_3). Anal. Calcd $C_{13}H_{12}N_2O_2S$ (260.31): C, 59.98; H, 4.65; N, 10.76. Found: C, 60.13; H, 4.80; N, 10.57.

1-(5′-Bromofuroyl)-3-methyl-3-phenylthiourea (2b). 81% yield (from acetone–H_2O), mp 136–137°C; ν_{max}/cm^{-1} 3350 (N–H), 3030 (C–H), 2900 (C–H), 1687 (C=O), 1605 (C=C), 1570 (band I, N–C=S), 1410 (band II, N–C=S), 1165 (band III, N–C=S) and 935 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.72 (1H, s, NH), 7.50–7.41 (5H, m, Ph), 6.12 (1H, d, H3, J=3.8 Hz), 5.79 (1H, d, H4, J=3.8 Hz), 3.4 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ173.0 (CS), 161.0 (CO), 151.3 (C2), 144.2 (C1′), 129.4 (2C), 126.0 (C5), 118.9, 116.2 (C4), 114.3 (C3), 113.1 (2C) and 46.1 (CH_3). Anal. Calcd $C_{13}H_{11}BrN_2O_2S$ (339.21): C, 46.03; H, 3.27; N, 8.26. Found: C, 46.33; H, 3.50; N, 8.32.

1-Furoyl-3,3-dibenzylthiourea (2c). 83% yield (from acetone–H_2O), mp 146–147°C; ν_{max}/cm^{-1} 3320 (N–H), 3020 (C–H), 2910 (C–H), 1693 (C=O), 1608 (C=C), 1580 (band I, N–C=S), 1425 (band II, N–C=S), 1173 (band III, N–C=S) and 928 (band IV, N–C=S); ^{1}H NMR (DMSO-d_6) δ 8.71 (1H, s, NH), 7.63 (1H, d, H5, J=2.1 Hz), 7.32–7.52 (10H, m, Ph), 7.1 (1H, d, H3, J=3.2 Hz), 6.6 (1H, m, H4), 5.2 (2H, s, CH_2) and 4.7 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 189.8 (CS), 153.9 (CO), 147.6 (C2), 145.5 (C5), 138.4, 136.9, 129.1 (2C), 128.8 (2C), 128.5 (2C), 128.4 (2C), 127.7, 127.5 (aromatics), 117.6 (C3), 112.9 (C4), 56.1 (CH_2) and 55.3 (CH_2). Anal. Calcd $C_{20}H_{18}N_2O_2S$ (350.43): C, 68.55; H, 5.18; N, 8.20. Found: C, 68.68; H, 5.35; N, 8.29.

Alkylation of 1-acyl-3,3-dialkylthioureas

1-Acyl-3,3-dialkylthioureas were alkylated by the method reported in the literature[3] using dimethyl or diethyl sulphate as alkylating agent (the methylated thioureas were **1c**–**1e** and **2a**–**2c**, the ethylated ones were **1a** and **1b**). Potassium carbonate was used as catalyst and dimethylformamide as solvent. The relative rates of reaction for each isomer were determined from the reaction mixtures resulting from the alkylation of the different thioureas, using the values of the sum of the integrals derivated from the ^{1}H NMR spectra. The formula $(I_S+I_N+I_O)/I_X=100\%/\boldsymbol{X}\%$, where each index represents one of the studied isomers, was used.

^{1}H NMR showed that the methylated products exhibit the following chemical shift for the methyl protons of the isomers –S–CH_3, –N–CH_3, –O–CH_3, δ: **1c**: 2.34, 2.79, 2.82; **1d**: 2.35, 2.80, 2.84; **1e**: 2.30, 2.86, 2.92; **2a**: 2.60, 2.80, 2.90; **2b**: 2.30, 2.80, 2.90; **2c**: 2.40, 2.81, 2.90. The ethylated products showed the chemical shift for the methylene protons of the isomers –S–CH_2CH_3, –N–CH_2CH_3, –O–CH_2CH_3, δ: **1a**: 2.90, 4.13, 4.37; **1b**: 2.95, 3.40, 4.00.

By means of ^{13}C NMR it was determined that the methylated products exhibits the following chemical shifts for the methyl carbons of the isomers –S–CH_3, –N–CH_3, –O–CH_3, δ: **1c**: 15.9, 31.3, 36.1; **1d**: 14.9, 28.9, 35.5; **1e**: 12.8, 28.9, 33.6; **2a**: 16.1, 31.1, 36.1; **2b**: 16.6, 29.9, 33.1; **2c**: 16.3, 28.9, 35.2. For the ethylated products the chemical shifts for the methylene carbons of the isomers are S–CH_2CH_3, N–CH_2CH_3, O–CH_2CH_3, δ: **1a**: 27.2, 43.5, 63.5; **1b**: 27.2, 43.5, 63.5.

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