Acyl C→N migration in the thioureidomethylation of 2-(4-methylbenzoyl)cyclohexanone

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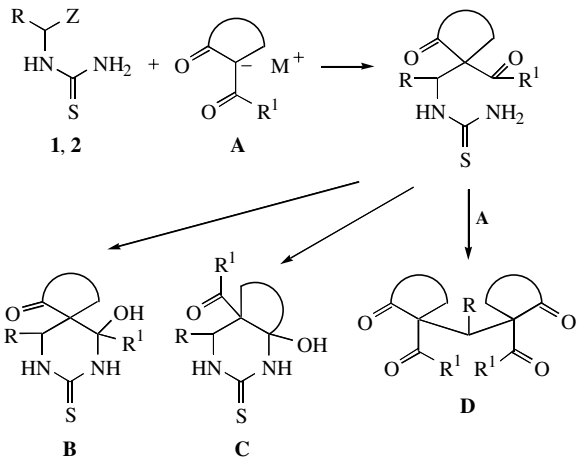
The thioureidomethylation of the sodium enolate of 2-(4-methylbenzoyl)cyclohexanone 3 with *N*-(tosylmethyl)thiourea 1a or *N*-(azidomethyl)thiourea 2 in acetonitrile results in the unexpected formation of *N*-(4-methylbenzoyl)-*N′*-[(2-oxocyclohexyl)-methyl]thiourea 6, which was structurally characterised by X-ray diffraction analysis.

Recently, we reported a convenient general synthesis of 5-acyl and 5-alkoxycarbonyl substituted 4-hydroxyhexahydropyrimidine-2-thiones from readily available *N*-(1-tosyl-1-alkyl)thioureas **1** (R = H, alkyl, aryl) or *N*-(azidomethyl)thiourea **2** (R = H) and the enolates of acyclic 1,3-diketones and β-oxoesters, respectively.[1–3] In contrast, the reaction of **1** and **2** with the enolate of a cyclic 1,3-diketone such as dimedone gave methylene-bis-(dimedone) rather than the expected bicyclic pyrimidine-2-thione.[4] No other cyclic 1,3-dicarbonyl compounds, in particular, those bearing an exocyclic carbonyl group (**A**), were studied in this reaction. Based on our previous data, at least three different reactions can occur in this case to give spiro heterocycles **B**, fused heterocycles **C** and bis-alkylation products **D** (Scheme 1).



1, **2** **A** **B** **C** **D**

1 Z = Ts, R = H, alkyl, aryl
2 Z = N_3, R = H
R^1 = alkyl, aryl; M = K, Na

Scheme 1

Here, we report on the reactivity of *N*-(tosylmethyl)thiourea **1a** (R = H)† and *N*-(azidomethyl)thiourea **2**† towards the sodium enolate of 2-(4-methylbenzoyl)cyclohexanone generated by the treatment of corresponding CH acid **3** with one equivalent of sodium hydride in dry acetonitrile (Scheme 2).

Using thin layer chromatography,‡ we found that the reaction of **1a** with an equimolar amount of the sodium enolate of **3** in acetonitrile at room temperature results in the disappearance of **1a** in a short time (~7 h). According to TLC, the reaction mixture mainly consists of starting CH acid **3** and a new low polar product. A mixture of these compounds in a 40:60 ratio (^{1}H NMR spectroscopy data) was isolated after the evaporation of the solvent in a vacuum followed by the successive treatment of the residue with light petroleum, a saturated aqueous $NaHCO_3$ solution and chloroform. The resulting mixture was separated by the extraction of CH acid **3** with boiling hexane.§

The preliminary structure of the product was determined by IR and ^{1}H and ^{13}C NMR spectroscopy.¶ These data disagreed with the expected structures of **4** and **5** containing a 4-hydroxyhexahydropyrimidine-2-thione moiety. The absence of this moiety (see ref. 2,3) followed, in particular, from the character of absorption at 1500–1700 cm^{-1} in the IR spectrum of the substance obtained. Furthermore, the signal of the proton of the OH group was not observed at 5.80–6.10 ppm (see ref. 2,3) in the ^{1}H NMR spectrum in [$^2H_6$]DMSO.

Spectroscopic data and the results of elemental analysis were consistent with the structures of two isomeric compounds, *N*-acylthiourea **6** and 10-membered cyclic thioureide **7**. However, it was impossible to choose **6** or **7** unambiguously on the basis of the data obtained. This choice in favour of *N*-(4-methylbenzoyl)-*N′*-[(2-oxocyclohexyl)methyl]thiourea **6** was made by a single crystal X-ray diffraction study.††

Figure 1 shows the X-ray structure of compound **6** and the numbering of atoms. A characteristic feature of **6** is a planar structure of its thioureidomethyl fragment connecting phenyl and cyclohexane rings. The hydrogen atom of the N(1)–H

† Compound **1a** was prepared by the reaction of *N*-(hydroxymethyl)-thiourea[6] with *p*-toluenesulfinic acid in water at 20 °C according to a published procedure.[5] Crude product **1a** obtained in this reaction was used without further purification. ^{1}H NMR (Bruker DPX 300, 300.13 MHz, [$^2H_6$]DMSO) δ: 8.36 (unsolved br. t, 1H, NH), 7.77 (br. s, 1H, NH in NH_2), 7.70 (d, 2H, C_{arom}, *J* 8.1 Hz), 7.43 (d, 2H, C_{arom}, *J* 8.1 Hz), 7.16 (br. s, 1H, NH in NH_2), 5.17 (br. d, 2H, CH_2, *J* ~ 5 Hz), 2.40 (s, 3H, Me). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 183.97 (C=S), 144.54 [C(4) in Ts], 134.79 [C(1) in Ts], 129.75 [C(3) and C(5) in Ts], 128.51 [C(2) and C(6) in Ts], 64.81 (CH_2), 21.13 (Me). IR (Shimadzu IR 435, Nujol, ν/cm^{-1}): 3392, 3291, 3180 (ν N–H), 3077, 3041 (ν C_{arom}–H), 1608, 1548 [NH–C(S)–NH_2], 1271 (ν_{as} SO_2), 1133 (ν_s SO_2), 802 (δ C_{arom}–H).

Compound **2** was synthesised according to a modified method:[2] a mixture of *N*-(hydroxymethyl)thiourea[6] (13.34 g, 125.7 mmol), NaN_3 (13.89 g, 213.7 mmol) and water (40 ml) was cooled to –10 °C and treated dropwise under stirring with a solution of conc. HCl (18.0 ml, 21.24 g, 209.7 mmol) in water (20 ml) for 10 min (all operations for the synthesis of **2** should be carried out in a hood). The flask was closed with a glass stopper, and the reaction mixture was stirred at room temperature for 2 h. Then seed crystals of **2** were added to the solution obtained (otherwise crystallization begins later). Immediately abundant white precipitate of **2** starts to separate out. The reaction mixture was additionally stirred at room temperature for 4.5 h, allowed to stand at the same temperature for 14 h, and cooled to +5 °C. The solid was collected by filtration, washed with ice water and light petroleum and dried to afford 13.25 g (80.4%) of **2**, which was used without further purification. ^{1}H NMR (Bruker DPX 300, 300.13 MHz, [$^2H_6$]DMSO) δ: 8.33 (br. s, 1H, NH), 7.62 (br. s, 2H, NH_2), 4.89 (br. s, 2H, CH_2). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 184.68 (C=S), 59.14 (CH_2). IR (Shimadzu IR 435, Nujol, ν/cm^{-1}): 3357, 3263, 3164, 3048 (ν NH), 2082 (ν N3), 1608, 1568 [NH–C(S)–NH_2], 1348, 1273, 1221.

‡ TLC was performed on Silufol UV-254 silica gel plates using chloroform or chloroform–methanol (9:1, v/v) as an eluent; the plates were visualised with iodine vapour.

group and the O(41) atom form a strong intramolecular hydrogen bond,‡‡ the geometrical parameters of which are shown in Figure 1. The hydrogen atom of the N(1)–H group is located (within the limits of 0.01 Å) in the plane of non-hydrogen atoms of the acylthiourea moiety. As a result, the second flat six-membered ring that includes the atoms O(41), C(4), N(3), C(2) and N(1) and the hydrogen atom of the N(1)–H group is

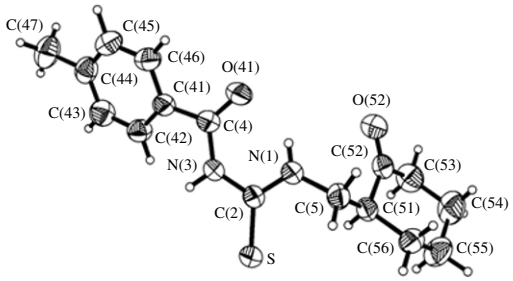


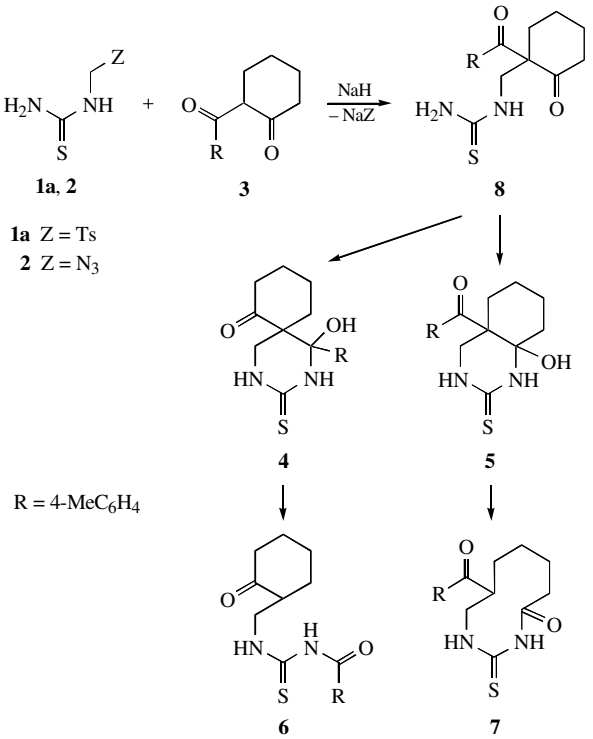
Figure 1 Molecular structure of compound **6** and the intramolecular hydrogen bond N(1)–H···O(41). Parameters of the hydrogen bond: N(1)···O(41) 2.673(2) Å, H(N1)···O(41) 2.00(2) Å, the angle N(1)–H···O(41) is equal to 139(2)°.

simulated in the molecule of **6**. A similar presence of an intramolecular hydrogen bond in the ureide fragment is observed in the structure of *N*-benzoyl-*N*′-(5-phenyl-1,3,4-oxadiazol-2-yl)-urea.[8]

Thus, the main direction of the reaction of *N*-(tosylmethyl)-thiourea **1a** with the sodium enolate of CH acid **3** in acetonitrile is the formation of *N*-(4-methylbenzoyl)-*N*′-[(2-oxocyclohexyl)-methyl]thiourea **6**. The yield of isolated compound **6** on the basis of reacted thiourea **1a** was relatively low and in various experiments did not exceed 24% (yield of crude **6** was about 34% according to ^{1}H NMR spectroscopy data). Note that a significant quantity of charged CH acid **3** (about 22%) did not react and it was recovered after the treatment of reaction mixtures. Apparently, it is caused by partial transformation of nucleophilic sodium enolates of **3** in the loose CH acid under the action of thioureide **6** with rather high NH acidity.§§

The reaction of *N*-(azidomethyl)thiourea **2** with **3** (NaH, acetonitrile, 20 °C) provided analogous results. Thioureide **6** was isolated in 14% yield as the principal product of the reaction.

The synthesis of **6** proceeds, apparently, through a stage of the initial formation of thioureidomethylation product **8**, which predominantly undergoes cyclization into 1-hydroxy-1-(4-methylphenyl)-3-thioxo-2,4-diazaspiro[5.5]undecane-7-one **4**.¶¶ The latter spontaneously turns into thioureide **6** after



Scheme 2

§ *Synthesis of* **6**: a 50 ml round-bottom flask fitted with a magnetic stirring bar and calcium chloride drying tube was charged with NaH (0.133 g, 5.55 mmol) and dry acetonitrile (10 ml). Compound **3** (1.202 g, 5.56 mmol) was added in one portion with stirring, and the resulting mixture was stirred with protection from air moisture at room temperature up to the finishing of hydrogen evolution (about 2 h). To the resulting suspension of sodium enolate of **3** was added thiourea **1a** (1.358 g, 5.56 mmol) and dry acetonitrile (7 ml). The flask was sealed with a glass stopper, and the reaction mixture was stirred at room temperature for 7 h. The solvent was removed under a reduced pressure, and the residue was treated with light petroleum (6 ml) at room temperature for 1 h. After decanting the light petroleum, a saturated aqueous solution of $NaHCO_3$ (3 ml) was added, and the gummy substance obtained was rubbed up to complete solidification. The precipitate was filtered, washed with cold water and light petroleum and dried. The solid obtained (1.499 g) was treated with chloroform (30 ml); the solution was filtered from an insoluble residue and vacuum evaporated to dryness. Then, hexane (3 ml) was added; the precipitate was collected by filtration and dried to give a mixture (0.838 g) of compounds **6** (33.7% according to ^{1}H NMR spectroscopy data) and **3** (60:40). The mixture obtained was extracted with boiling hexane (6×5 ml). The hexane solution contained mainly CH acid **3**, and the insoluble residue was pure compound **6** (0.398 g, 23.6%). Mp 110–111 °C (ethanol). Found (%): C, 63.63; H, 6.17; N, 8.87. Calc. for $C_{16}H_{20}N_2O_2S$ (%): C, 63.13; H, 6.62; N, 9.20.

¶ *Spectroscopic data for* **6**. ^{1}H NMR (Bruker DPX 300, 300.13 MHz, [$^2H_6$]DMSO) δ: 11.17 (s, 1H, NH–C=O), 11.06 (br. t, 1H, N*H*–CH_2, $^3J_{NH,CH}$ 5.3 Hz), 7.83 (d, 2H, C(2)H and C(6)H in 4-MeC_6H_4, J 7.8 Hz), 7.31 (d, 2H, C(3)H and C(5)H in 4-MeC_6H_4, J 7.8 Hz), 3.72 (t, 2H, N–CH_2, $^3J_{CH,CH}$ 6.2 Hz, $^3J_{NH,CH}$ 5.3 Hz), 2.86 (m, 1H, CH–C=O), 2.32–2.53 (m, 1H, H_{ax} in CH_2–C=O, the signals partly overlapped with the signals of Me protons and residual protons of the solvent), 2.37 (s, 3H, Me), 2.18–2.29 (m, 1H, H_{eq} in CH_2–C=O, ^2J 13.4 Hz), 1.94–2.12 and 1.32–1.86 (2m, 2H and 4H, respectively, $CH_2CH_2CH_2$). ^{13}C NMR (Bruker DPX 300, 75.48 MHz, [$^2H_6$]DMSO) δ: 211.89 (C=O), 180.24 (C=S), 167.89 (NH–C=O), 143.48 [C(4) in 4-MeC_6H_4], 129.27 [C(1) in 4-MeC_6H_4], 129.04 [C(2) and C(6) in 4-MeC_6H_4], 128.64 [C(3) and C(5) in 4-MeC_6H_4], 48.73 (*C*H–C=O), 44.55 (CH_2–N), 41.42 (*C*H_2–C=O), 31.23 (*C*H_2CHC=O), 27.22 (*C*H_2CH_2C=O), 24.16 (*C*$H_2CH_2CH_2$C=O), 21.14 (Me). IR (FT-IR Bruker 'Equinox 55/S', KBr pellet, ν/cm^{-1}): 3251 (ν NH), 3049 (ν C_{arom}–H), 1712 (ν C=O), 1672 (amide-I), 1612 (ν C=C), 1560, 1520, 1500 (amide-II, thioamide-II), 1257, 1163, 746.

†† *Crystal data.* The triclinic single crystals of **6** belong to space group $P\bar{1}$, a = 10.787(2), b = 10.565(2), c = 8.273(2) Å, α = 106.09(1)°, β = = 104.08(1)°, γ = 101.66(1)°, V = 841.1(3) Å^3, Z = 2, d_{calc} = 1.202 g cm^{-3}; $C_{16}H_{20}N_2O_2S$, M = 304.40. Intensities of 2786 independent reflections were measured with a Syntex P2$_1$ four-circle diffractometer (CuKα radiation, graphite monochromator, $\theta/2\theta$ scanning technique, θ_{min} = 4.41°, θ_{max} = 63.68°), 2521 reflections have $I > 2\sigma(I)$. The absorption correction was introduced by the semiempirical method using a transmission curve. The structure was solved by the direct method; non-hydrogen atoms were refined by the full-matrix least-squares procedure in the anisotropic approximation. The coordinates of all hydrogen atoms were located from the difference electron-density maps and refined by the least-squares procedure isotropically. The final value of the discrepancy factor R = 0.041 was calculated for 2521 reflections with $I > 2\sigma(I)$ (R = 0.044 for 2786 independent reflections). All calculations were performed using the SHELX97 program.[7]

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 223321. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

‡‡ According to ^{1}H NMR spectroscopy data, this intramolecular hydrogen bond also occurs in solutions of **6**. Indeed, when turning from a solution in $CDCl_3$ to a solution in [$^2H_6$]DMSO the expected significant downfield shift of NH protons in the NH–C=O fragment of **6** occurs (from δ 8.91 to 11.17 ppm), while the chemical shift of NH protons in the NH–CH_2 fragment does not change (δ 11.06 ppm in both solvents).

§§ For example, the five-membered cyclic thioureide 2-thiohydantoine has pK_a 8.51 (water, 25 °C) due to the deprotonation of the N(3)H group.[9]

cleaving the C(1)–C(6) bond of the hexahydropyrimidine ring under the reaction conditions. Thus, the transformation **8** → **6** can be considered as the C→N migration of the 4-methylbenzoyl group.†††

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¶¶ This preferable direction of heterocyclization is unexpected because of a well-known fact of greater reactivity of aliphatic ketones in comparison with aromatic ones in reactions with nucleophiles. Recently, we found[2] that the reaction of **1a**, **2** with benzoylacetone (NaH, acetonitrile, 20 °C) results in the exclusive formation of 5-benzoyl-4-hydroxy-4-methylhexahydropyrimidine-2-thione, which is a heterocyclization product with the participation of an acetyl group rather than a benzoyl group in the initial product of benzoylacetone thioureidomethylation.

††† Earlier, an analogous base-catalysed transformation was found in the series of 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones.[10]

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