Reaction of Cyclic Thioureas with 2-Benzylidenecycloalkanones

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$BF_3 \cdot OEt_2$-catalyzed reaction of cyclic thioureas (1) with 2-benzylidenecycloalkanones (2) afforded tricyclic 1,3-thiazines (3, 4). The progress of the reactions was found to depend on the ring size of both 1 and 2.

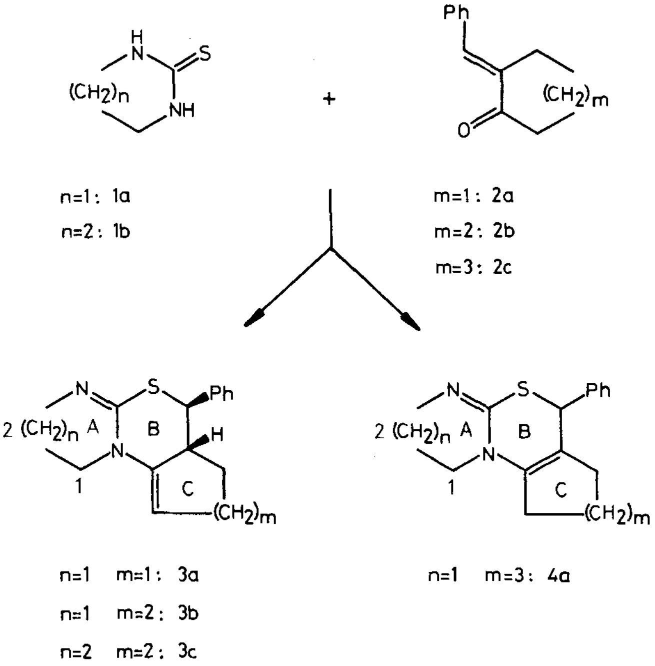
While the acid-catalyzed reaction of α,β-unsaturated carbonyl compounds with thiourea has been known for long[1], the similar reaction of cyclic thioureas has hardly been investigated. In the only case 2-imidazolidinethione was treated with α,β-unsaturated carbonyl compounds in the presence of hydrochloric acid as catalyst; these experiments, however, failed to give the expected 1,3-thiazine derivatives[2].

In continuation of our synthetic and stereochemical investigations on the reactions of cyclic α,β-unsaturated ketones with thiocarbonic acid derivatives[3], we were interested in elaborating the ring closure of 2-benzylidenecycloalkanones with cyclic thioureas. In these reactions formation of tricyclic 1,3-thiazine derivatives was supposed, which were interesting from both pharmacological and chemical aspects[4].

Cyclic thioureas **1a**, **b** were treated with 2-benzylidenecycloalkanones **2a**–**c** in absolute chloroform in the presence of $BF_3 \cdot OEt_2$ as catalyst. The progress of the reactions strongly depends on the ring size of both the cyclic thioureas and the α,β-unsaturated ketones. Thus with 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethione (**1b**) the ring closure took place only with **2b** to give **3c**. The other unsaturated ketones did not react with **1b**, even not with longer reaction times nor higher temperatures.

An interesting selectivity was observed concerning the location of the carbon-carbon double bond in the compounds obtained. The reaction of **2a** and **2b** led to the formation of compounds **3a**–**c** containing the double bond in the ring C. Under similar conditions **2c** gave **4a** in which the double bond is located between the annelated carbon atoms of B/C rings (Scheme)[5].

^{1}H-NMR analysis of the crude products showed that in all reactions only one of the possible isomers had been formed. In the IR spectra the lack of the νC=O and the νOH bands is unambiguous evidence of the progress of the condensation reactions. This was also supported by mass spectrometric studies. The mass spectra of compounds **3** and **4** (see Experimental) exhibited abundant peaks of molecular ions, the exact masses of which were found to correspond to the structural formulae presented in the Scheme. The fragmentation patterns show closely related pictures and characteristic processes involving 1) selective cleavages of rings A and B, e.g. formation of ions at *m*/*z* 86 for **3a**, **3b**, and **4a** (five-membered ring A) and at *m*/*z* 100 for **3c** (six-membered ring A); 2) alkyl losses from ring C (e.g. $CH_3^{\bullet}$, $C_2H_5^{\bullet}$, and $C_3H_7^{\bullet}$ elimination from M^+ for **4a**).



Though in the above-mentioned type of reaction the attack of the soft nucleophilic sulfur of the cyclic thioureas at the β carbon of the reactant is expected[2], the angular constitution of the compounds was also corroborated by NMR methods. The ^{13}C-NMR spectra of compounds **3** and **4** strongly suggest this structure since the chemical shifts of the carbon atoms of the 1,3-thiazine rings support better the angular constitution than the alternative linear one[6]. ^{1}H-^{1}H 1D NOE investigations[7] gave further evidence in support of the structures: the NOE difference spectra display the most remarkable enhancement of the signals of 8-H (12%), 9-H (15%), 10-H (21%), and 10-H (8%) for compounds **3a**, **3b**, **3c**, and **4a**, respectively, during the saturation of the signal of the 1-H protons.

The isomeric structures **3** and **4** can be easily distinguished on the basis of the sign of the benzylic proton, which is a singlet for **4a** and shows a doublet for **3a**–**c**. The magnitudes of $^3J_{5,5a}$ and $^3J_{6,6a}$ (≈11 Hz) for **3a**, **b** and **c**, respectively, are in agreement with a dihedral angle being either about 0° or 180°[8]. On considering the dihedral angles in each conformation of the possible configurational isomers of **3b** and **3c**, these vicinal coupling constants indicate the antiperiplanar position of these methine protons, i.e. the *trans* configuration of these compounds.

In the ^{1}H-NMR spectra of **3a** the relatively large (2.1 Hz) $^4J_{8,5a}$ allylic coupling constant suggests the proton 5a-H to be axial to the heteroring, i.e. the conformation of the B/C ring is C-outside. The diaxial steric interaction discussed above, however, can occur

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in the boat (with dihedral angle of about 10°) or in the chair (with dihedral angle of about 170°) conformation of the 1,3-thiazine ring with *cis* or *trans* configuration, respectively. So in this case additional ^{1}H-^{1}H 1D NOE measurements were carried out in order to solve the problem of the relative configuration. Saturation of the resonance signal of 6-H_{ax} (which was assigned to be in axial position on the basis of its coupling constants showing three diaxial interactions) enhanced the signal of 5-H (9%), while the saturation of the resonance signal of 6-H_{eq} enhanced the signal of 5a-H (8%). These observations corroborate the *trans* configuration of **3a**.

It is worth mentioning that the determination of the relative configuration of C-5 and C-5a (similarly to that of C-6 and C-6a in **3c**) is not possible on the basis of the ^{13}C-NMR spectra, however, the similar carbon chemical shifts of the phenyl groups and those of the C-5 or C-6 atoms (in **3a**, **b** and **c**, respectively) point to identical relative configuration of these compounds, too[9].

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Experimental

Melting points are uncorrected. – IR spectra: Specord 75 IR. – Mass spectra: AEI MS-902 (70eV). – ^{1}H- and ^{13}C-NMR spectra: Bruker WP-200 ($CDCl_3$, TMS as internal standard, 50.28 and 200 MHz for ^{13}C and ^{1}H NMR, respectively. – ^{1}H-^{1}H 1D NOE measurements: ASPECT 2000 micro program, D1 = 10s, D2 = 2ms). – Kieselgel Merck (70–230 mesh).

General Procedure: Compounds **1a**, **b** (0.020 mmol) were suspended in 100 ml of absol. $CHCl_3$ solution of unsaturated ketone **2a–c** (0.020 mol). The mixture was cooled to –5°C and $BF_3 \cdot OEt_2$ (0.040 mol) was added dropwise with stirring during 1/2 h. It was stirred with cooling for additional 2 h, then the stirring was continued at room temperature. After completing the reaction (5–10 days) the mixture was cooled and made alkaline with 25% NH_3 solution. The aqueous solution was separated, extracted with $CHCl_3$ and the combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. The oily residue was chromatographed over silica (benzene as eluent) to give a solid. It was recrystallized to yield colourless crystals of **3** and **4**.

trans-1,2,5,5a,6,7-Hexahydro-5-phenylcyclopent[d]imidazo[2,1-b][1,3]thiazine (**3a**): Yield 2.95 g (58%), m.p. 129–131°C (petroleum ether). – IR (CCl_4): 2930/2850 cm^{-1} (CH), 1645 (C=N), 1570 (C=C). – ^{1}H NMR: δ = 7.38–7.28 (m; 5H, aromatic H), 4.58 (dt, ${}^{4}J_{8,5a}$ = 2.1, ${}^{3}J_{8,7}$ = 4.5 Hz; 1H, 8-H), 4.07 (d, ${}^{3}J_{5,5a}$ = 11.2 Hz; 1H, 5-H), 4.10–3.58 (m; 4H, 1,2-H), 3.48–3.32 (m; 1H, 5a-H), 2.35–2.25 (m; 2H, 7-H), 1.99–1.84 (m; 1H, 6-H_{eq}), 1.53–1.32 (m, ${}^{2}J_{6ax,6eq}$ = 12.8, $|{}^{3}J_{6ax,7eq} + {}^{3}J_{6ax,7ax}|$ = 19.0, ${}^{3}J_{6ax,5a}$ = 9.6 Hz; 1H, 6-H_{ax}). – ^{13}C NMR: δ = 156.3 (C-3a), 140.3 (C-8a), 137.2 (C-1′), 128.9^{a} (C-2′), 128.4 (C-4′), 128.2^{a} (C-3′), 99.6 (C-8), 53.2 (C-2), 50.5 (C-5), 48.1 (C-5a), 47.3 (C-1), 29.7^{b} (C-6), 28.3^{b} (C-7); a, b alternative assignment also possible. – MS: *m/z* (%) = 257(21), 256(100, M^+), 255(26), 228(3), 227(3.5), 223(5), 215(3.5), 184(15), 139.0349 (64, $C_6H_7N_2S^+$), 117(3), 115(7), 91(15), 86.0058 (68, $C_3H_4NS^+$).

$C_{15}H_{16}N_2S$ (256.4) Calcd. C 70.28 H 6.29 S 12.51
Found C 70.15 H 6.35 S 12.47

trans-1,2,5a,6,7,8-Hexahydro-5-phenyl-5H-imidazo[1,2-a][3,1]benzothiazine (**3b**): Yield 3.20 g (59%), m.p. 168–171°C (ether). – IR (CCl_4): 2940/2855 cm^{-1} (CH), 1645 (C=N), 1570 (C=C). – ^{1}H NMR: δ = 7.43–7.26 (m; 5H, aromatic H), 4.77 (dt, ${}^{4}J_{9,5a}$ = 1.3, ${}^{3}J_{9,8}$ = 4.0 Hz; 1H, 9-H), 4.07 (d, ${}^{3}J_{5,5a}$ = 11.1 Hz; 1H, 5-H), 3.95–3.58 (m; 4H, 1,2-H), 2.95–2.87 (m; 1H, 5a-H), 2.56–1.04 (m; 6H, 8,7,6-H). – ^{13}C NMR: δ = 155.4 (C-3a), 137.4 (C-9a), 136.1 (C-1′), 128.7^{a} (C-2′), 128.2 (C-4′), 128.1^{a} (C-3′), 101.1 (C-9), 57.8 (C-2), 52.2 (C-1), 48.8 (C-5), 41.4 (C-5a), 27.8^{b} (C-6), 24.1^{b} (C-8), 21.6 (C-7); a, b alternative assignment also possible. – MS: *m/z* (%) = 271(22), 270(100, M^+), 269(24), 242(9), 241(6), 237(4), 227(2), 212(2), 198.1274(7, $C_{14}H_{16}N^+$), 185(7), 184(5), 170.0922 (10, $C_{12}H_{12}N^+$), 117.0716 (19, $C_9H_9^+$), 115(9), 91(20), 86(19).

$C_{16}H_{18}N_2S$ (270.4) Calcd. C 71.07 H 6.71 S 11.86
Found C 70.92 H 6.85 S 11.75

trans-2,3,6a,7,8,9-Hexahydro-6-phenyl-1H,6H-pyrimido[1,2-a][3,1]benzothiazine (**3c**): Yield 3.95 g (69%), m.p. 170–172°C (ether). – IR (CCl_4): 2940/2855 cm^{-1} (CH), 1630 (C=N), 1590 (C=C). – ^{1}H NMR: δ = 7.39–7.24 (m; 5H, aromatic H), 5.09 (t, ${}^{3}J_{10,9}$ = 7.6 Hz; 1H, 10-H), 4.11 (d, ${}^{3}J_{6,6a}$ = 11.2 Hz; 1H, 6-H), 3.63–3.30 (m; 4H, 1,3-H), 2.78–2.65 (m; 1H, 6a-H), 2.19–1.08 (m; 8H, 9,2,8,7-H). – ^{13}C NMR: δ = 150.9 (C-4a), 140.1 (C-10a), 138.1 (C-1′), 128.7^{a} (C-2′), 128.6^{a} (C-3′), 127.9 (C-4′), 104.2 (C-10), 49.5 (C-6), 46.5 (C-3), 45.1 (C-1), 42.0 (C-6a), 27.8^{b} (C-7), 24.7^{b} (C-9), 22.6 (C-2), 20.4 (C-8); a, b alternative assignment also possible. – MS: *m/z* (%) = 285(21), 284.1205 (100, M^+, $C_{17}H_{20}N_2S^+$), 283(19), 255(12), 251(10), 226(12), 212(4), 198(11), 193(5), 184(6), 148(7), 134(6), 117(10), 115(9), 100.0220 (12, $C_4H_6NS^+$), 91(19), 71.9950 (23, $C_2H_2NS^+$).

$C_{17}H_{20}N_2S$ (284.4) Calcd. C 71.79 H 7.09 S 11.27
Found C 71.58 H 7.21 S 11.14

1,2,5,6,7,8,9,10-Octahydro-5-phenylcyclohept[d]imidazo[2,1-b]-[1,3]thiazine (**4a**): Yield 3.80 g (67%), m.p. 122–124°C (ether). – IR (CCl_4): 2925/2850 cm^{-1} (CH), 1650 (C=N), 1570 (C=C). – ^{1}H NMR: δ = 7.29–7.15 (m; 5H, aromatic H), 4.37 (s; 1H, 5-H), 3.97–3.60 (m; 4H, 1,2-H), 2.51 (t, ${}^{3}J_{10,9}$ = 5.3 Hz; 2H, 10-H), 2.49–2.07 (m; 2H, 6-H), 1.75–1.28 (m; 6H, 9,8,7-H). – ^{13}C NMR: δ = 156.1 (C-3a), 141.8 (C-10a), 137.6 (C-1′), 128.4^{a} (C-2′), 127.1 (C-4′), 127.0^{a} (C-3′), 111.6 (C-5a), 52.6 (C-2), 48.4 (C-5), 47.4 (C-1), 33.5 (C-6), 31.3 (C-9), 30.1 (C-10), 26.6 (C-7), 25.0 (C-8); a, b alternative assignment also possible. – MS: *m/z* (%) = 285(22), 284(100, M^+), 283 (71), 256(4), 255(6), 251(14), 241(38), 230.0855 (7, $C_{13}H_{14}N_2S^+$), 227(8), 224.1421(9, $C_{16}H_{18}N^+$), 212(22), 193(19), 141(10), 117(12), 115(21), 91(29), 86(28).

$C_{17}H_{20}N_2S$ (284.4) Calcd. C 71.79 H 7.09 S 11.27
Found C 71.83 H 7.17 S 11.19

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