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Synthesis of 1,3-thiazoline derivatives from β-dicarbonyl compounds and phenacyl thiocyanate

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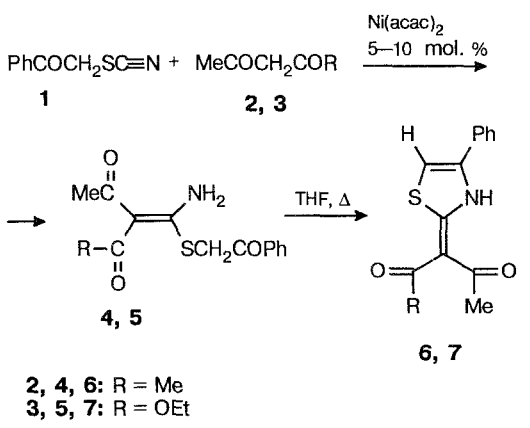
Acetylacetone and ethyl acetoacetate undergo addition at the C≡N bond of phenacyl thiocyanate in the presence of $Ni(acac)_2$ to give the respective ketene *N,S*-acetals, which undergo smooth cyclization to afford 2-methylene-4-phenyl-1,3-thiazoline derivatives when refluxed in THF .

Key words: phenacyl thiocyanate, β-dicarbonyl compounds, ketene *N,S*-acetals, nickel acetylacetonate, 1,3-thiazoline derivatives, boron chelates.

Previously[1] we suggested a convenient procedure for the preparation of diacyl- and alkoxycarbonyl(acyl)-ketene *N,S*-acetals from esters of thiocyanic acid and β-diketones or esters of β-ketoacids in the presence of catalytic amounts of $Ni(acac)_2$. *N,S*-Acetals of this type were shown to be suitable starting reagents for synthesizing heterocyclic compounds.[2,3] Therefore, it seemed interesting to use functionally substituted thiocyanates in reactions with β-dicarbonyl compounds, since the formation of the respective *N,S*-acetals capable of direct heterocyclization could be expected in some cases.

The reaction of phenacyl thiocyanate (**1**) with acetylacetone (**2**) and ethyl acetoacetate (**3**) was studied in this work. Attempts to perform the addition of compounds **2** and **3** to thiocyanate **1** without a catalyst or in the presence of a base (MeONa) were unsuccessful. However, the above β-dicarbonyl compounds smoothly undergo addition to the C≡N bond of thiocyanate **1** under mild conditions in the presence of $Ni(acac)_2$, which results in the respective *N,S*-acetals (**4,5**).



The structures of the resulting compounds were confirmed by spectroscopic data. For example, the mass spectra for reaction products **4—7** display molecular ion peaks. The IR spectra for compounds **4** and **5** display absorption characteristic of free NH groups and those involved in intramolecular hydrogen bonds (a band at

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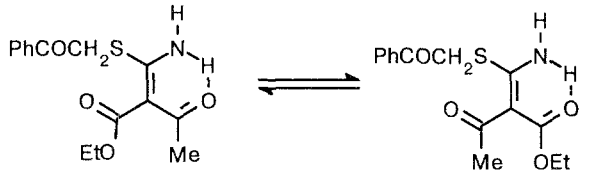
3580 cm^{-1} and broad diffuse bands in the 3400—2900 cm^{-1} region, respectively). The free and bonded NH groups are manifested in the ^1H NMR spectra (in $CDCl_3$) as two singlets of equal intensities ($\delta \approx 5$—6 and 10—12, respectively), and the signal for the SCH_2 group in compound **4** is observed as a quadruplet (an AB-spectrum). The spectrum for compound **5** displays two sets of signals of the NH_2 group, which indicates that a mixture of *E* and *Z* isomers is present,[1] whose ratio is ~1:3 (according to the NH signal intensities). It may be anticipated that compound **5**, like the *N,S*-acetal obtained from methyl thiocyanate and ethyl acetoacetate,[1] mostly consists of the *Z* isomer, in which the formation of the intramolecular hydrogen bond involves the acetyl group.



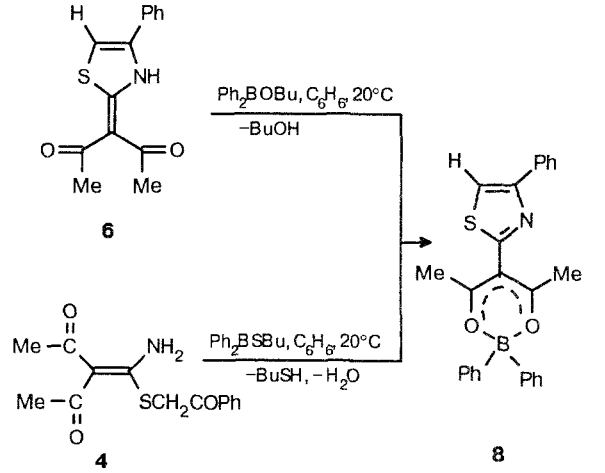
Z *E*

In the ^1H NMR spectrum for compound **5** in DMSO-d_6, the protons of each group are represented by one signal of the respective multiplicity (see Experimental), i.e., the spectrum becomes markedly simpler.

Compounds **4** and **5** readily abstract water on refluxing in THF and are smoothly transformed to the respective substituted thiazolines (**6**, **7**). The IR and ^1H NMR spectra of the latter display signals of NH groups, which makes it possible to rule out the tautomeric thiazole structure. The ^1H NMR spectrum ($CDCl_3$, 20 °C) for thiazoline **7**, which has different substituents at the exocyclic double bond, displays two signals in the ~2:1 ratio for each proton of the CH_3CO and NH groups (the multiplet for OCH_2 protons is complicated). This indicates that this compound, similarly to compound **5**, is a mixture of *E* and *Z* isomers with relatively slow mutual transformations. The spectrum for compound **7** in DMSO displays only one set of signals.

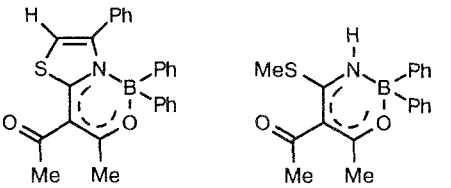
The synthesis of thiazolines **6** and **7** from thiocyanate **1** and dicarbonyl compounds can also be carried out without isolation of the intermediates, **4** and **5**. For example, refluxing a mixture of compounds **1** and **2** in THF in the presence of $Ni(acac)_2$ affords thiazoline **6** in 88 % yield.

The possibility of using compound **6** as a chelating ligand was shown: its reaction with Ph_2BOBu gave the diphenylboron chelate **8**. The latter is also formed in the reaction of *N,S*-acetal **4** with Ph_2BSBu. The IR spectrum for compound **8** contains no absorption bands of the NH group, while the mass spectrum contains a $[M]^+$ peak and a peak for the $[M-Ph]^+$ ion typical of boron chelates of this type.



6 **4** **8**

The ^1H NMR spectra for compound **8** contain one singlet (δ 2.33) for the CH_3CO group. ^{13}C NMR spectral data also indicate that the acetyl fragments are equivalent (there is one signal at δ 191.15 for both CO groups and one signal at δ 23.98 for both CH_3 groups). This suggests that they are involved in the coordination interaction with the boron atom and makes it possible to rule out the alternative structure **9**.



9 **10**

However, the boron atom in diphenylboron chelates of diacylketene *N,S*- and *N,N*-acetals is typically *N,O*-coordinated.[1,4] For example, the ^{13}C NMR spectrum for complex **10** displays two signals of carbonyl groups with chemical shifts of 196.86 ppm (free CO) and 182.89 ppm (CO→B) and two signals of MeCO with chemical shifts of 31.87 and 25.41 ppm. Evidently, structure **8** is stabilized due to the presence of the aromatic thiazole ring.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 radio-frequency spectrometer (δ). IR spectra were obtained on a UR-20 spectrophotometer ($CHCl_3$, ν/cm^{-1}). Mass spectra (*m/z*) were recorded on a Varian-MAT CH-6 spectrometer.

3-[Amino(phenacylthio)methylene]pentane-2,4-dione (4). A solution of thiocyanate **1** (0.8 g, 4.6 mmol), acetylacetone **2** (0.46 g, 4.6 mmol), and $Ni(acac)_2$ (0.09 g, 0.35 mmol, 8 %) in THF was stirred for 5 days at 20 °C under Ar. The course of the reaction was monitored by TLC and IR spectra (disap-

pearance of an absorption band for the C≡N group of the original compound **1**). Volatile compounds were removed *in vacuo*, and the residue was filtered through SiO_2 ($CHCl_3$ as the eluent). Removal of the solvent gave 1.25 g (98%) of practically pure (^1H NMR data) product **4** as a yellowish powder. Recrystallization from a benzene–hexane mixture (4:3) afforded 0.8 g (63%) of compound **4**, m.p. 128–131°C. Found (%): C, 60.31; H, 5.72; N, 5.07; S, 11.59. $C_{14}H_{15}NO_3S$. Calculated (%): C, 60.63; H, 5.45; N, 5.05; S, 11.57. IR: 3580 w (NH_{free}), 3450–2900 (NH_{bonded}, CH), 1630, 1570, 1560 (CO, C=C). ^1H NMR ($CDCl_3$): 12.18 (s, 1 H, NH_{bonded}), 7.54–7.37 (5 H, Ph), 5.92 (s, 1 H, NH_{free}), 3.26 (q, 2 H, SCH_2; AB-spectrum: H_A 3.22, H_B 3.30, J_{AB} = 12.4 Hz), 2.41 (s, 3 H, Me) and 2.37 (s, 3 H, Me). MS: 277 $[M]^+$, 259 $[M-H_2O]^+$.

Ethyl 2-[amino(phenacylthio)methylene]-3-oxobutanoate (5) was obtained similarly to *N,S*-acetal **4** from compounds **1** and **3**, yield 80%, m.p. 94–97°C (from benzene). Found (%): C, 58.72; H, 5.33; N, 4.81; S, 10.09. $C_{15}H_{17}NO_4S$. Calculated (%): C, 58.61; H, 5.58; N, 4.56; S, 10.43. IR: 3580 (NH_{free}), 3450–2915 (NH_{bonded}, CH), 1660–1640, 1580 (CO, C=C). ^1H NMR ($CDCl_3$): 12.30 and 10.65 (two br.s, 1 H, NH_{bonded}, ratio ~ 3 : 1), 7.65–7.30 (m, 5 H, Ph), 5.80 and 5.60 (two br.s, 1 H, NH_{free}, ratio ~ 3:1), 4.35–4.15 (m, 2 H, OCH_2), 3.40–3.20 (m, 2 H, SCH_2), 2.50 and 2.47 (two s, 3 H, MeCO), 1.30 (t, 3 H, $\underline{Me}CH_2$). ^1H NMR (DMSO-d_6): 12.30 and 10.43 (two br.s, 2 H, NH_2), 7.55–7.37 (m, 5 H, Ph), 4.18 (q, 2 H, OCH_2), 3.32 (s, 2 H, SCH_2), 2.35 (s, 3 H, MeCO), 1.28 (t, 3 H, $\underline{Me}CH_2$). MS: 307 $[M]^+$, 289 $[M-H_2O]^+$, 244 $[M-H_2O-OEt]^+$.

2-(Diacetylmethylene)-4-phenyl-1,3-thiazoline (6). a. *Cyclization of N,S-acetal* **4**. A solution of compound **4** (0.22 g, 0.8 mmol) in THF (6 mL) was refluxed for 40 h (TLC monitoring). After removal of the solvent the solid residue was recrystallized from a benzene–hexane mixture (3:4) to give 0.2 g (97 %) of thiazoline **6**, m.p. 146–147 °C. Found (%): C, 64.73; H, 5.06; N, 5.21; S, 12.08. $C_{14}H_{13}NO_2S$. Calculated (%): C, 64.84; H, 5.05; N, 5.40; S, 12.37. IR: 3500–3130 (NH), 3070, 2990, 2930 (CH), 1590, 1570 sh, 1540 (CO, C=C). ^1H NMR (DMSO-d_6): 14.86 (br.s, 1 H, NH), 7.83–7.70 and 7.56–7.35 (two m, 6 H, Ph and $CH_{thiazoline}$), 2.55 (s, 6 H, 2 Me). MS: 259 $[M]^+$.

b. *Direct synthesis from compounds* **1** *and* **2**. A solution of thiocyanate **1** (1.28 g, 7.2 mmol), diketone **2** (2.19 g, 21.9 mmol), and $Ni(acac)_2$ (0.19 g, 0.7 mmol, 10 %) in THF was stirred for one day at 20 °C, and then the reaction mixture was refluxed for 3 h. Recrystallization of the residue after removal of volatile compounds gave 1.55 g (88 %) of product **6**.

2-[Acetyl(ethoxycarbonyl)methylene]-4-phenyl-1,3-thiazoline (7) was obtained from *N,S*-acetal **5** similarly to thiazoline **6**, yield 85 %, m.p. 102–103 °C (from hexane). Found (%): C, 62.66; H, 5.69; N, 4.97; S, 11.11. $C_{15}H_{15}NO_3S$. Calculated (%): C, 62.26; H, 5.23; N, 4.84; S, 11.08. IR: 3410 (NH_{free}), 3300–2870 (NH_{bonded}, CH), 1695, 1640 (CO), 1585, 1565, 1555 (CO, C=C). ^1H NMR ($CDCl_3$): 17.0 and 13.8 (two br.s, 1 H, NH, ratio 2:1), 7.72–7.56 and 7.50–7.35 (two m, 5 H, Ph), 7.1 and 6.9 (two s, 1 H, $CH_{thiazoline}$), 4.42–4.30 (m, 2 H, OCH_2), 2.60 and 2.57 (two s, 3 H, MeCO), 1.46–1.35 (m, 3 H, $\underline{Me}CH_2$). ^1H NMR (DMSO-d_6): 15.1–14.3 (br.s, 1 H, NH), 7.70–7.60 and 7.55–7.40 (two m, 6 H, Ph and $CH_{thiazoline}$), 4.25 (q, 2 H, OCH_2), 2.45 (s, 3 H, MeCO), 1.30 (t, 3 H, $MeCH_2$). MS: 289 $[M]^+$, 244 $[M-OEt]^+$.

Diphenylboron 3(4-phenyl-1,3-thiazol-2-yl)pentane-2,4-dionate (8). a. A solution of thiazoline **6** (0.12 g, 0.46 mmol) and Ph_2BOBu (0.11 g, 0.46 mmol) in benzene (5 mL) was stirred for 4 h at 20 °C. Volatile compounds were removed *in vacuo*, then hexane was added to the residue. The crystals were filtered off, washed with hexane, and dried to give 0.13 g (69 %) of chelate **8**, m.p. 102–104 °C (from hexane). Found (%): C, 74.11; H, 5.36; B, 2.93; N, 3.55; S, 7.51. $C_{26}H_{22}BNO_2S$. Calculated (%): C, 73.76; H, 5.24; B, 2.56; N, 3.31; S, 7.57. IR: 1590, 1625 sh (CO, C=C). ^1H NMR: 7.90–7.98, 7.65–7.25, 7.15–6.75 (three m, 16 H, 3 Ph and $CH_{thiazole}$), 2.33 (s, 6 H, 2 Me). ^{13}C NMR, δ: 191.15 (q, $^2J_{C,H}$ = 6 Hz, 2 CO), 160.70 (q, $^3J_{C,H}$ = 8 Hz, SCN), 156.43 (m, C–Ph), 134.06, 133.44, 131.42, 128.95, 128.61, 127.42, 126.89, 126.47 (3 Ph), 117.41 (C-5), 115.51 (=C–H, $^1J_{C,H}$ = 186.5 Hz), 23.98 (q, 2 Me, $^1J_{C,H}$ = 130.0). MS: 423$[M]^+$, 346 $[M-Ph]^+$.

b. Chelate **8** (0.57 g, yield 80 %) was obtained similarly to the above procedure from *N,S*-acetal **4** (0.45 g, 1.6 mmol) and Ph_2BSBu (0.38 g, 1.6 mmol) in benzene.

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