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Mendeleev Commun., 2009, **19**, 52–53

Mendeleev Communications

Regiodirected synthesis of hydroazolic compounds with the use of thiosemicarbazide

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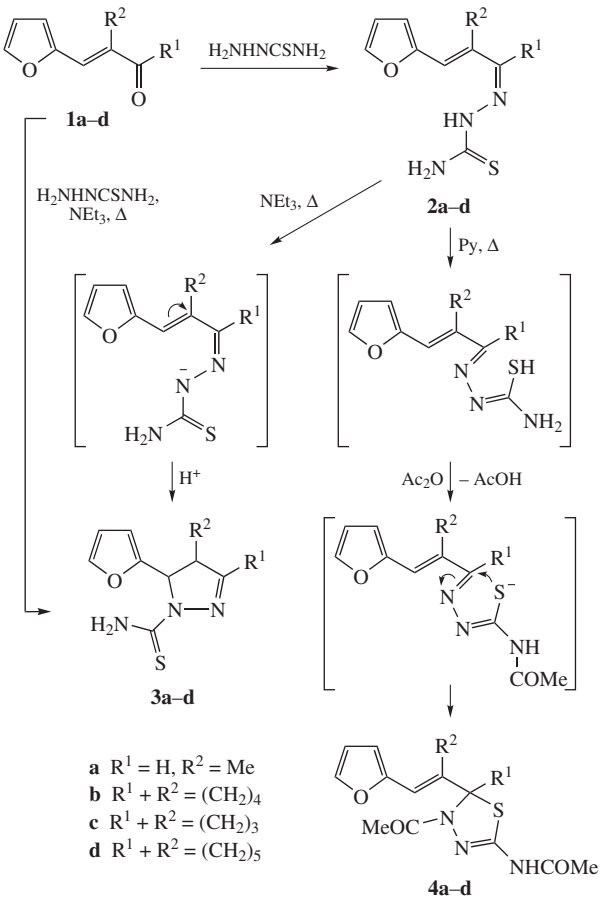
DOI: 10.1016/j.mencom.2009.01.021

Interaction of α,β-unsaturated ketones of furan series with thiosemicarbazide under basic catalysis leads to 3-furyl-2-thiocarbamoylpyrazolines since nitrous nucleophilic centre of a reagent is activated, whereas the products of intermolecular cyclization of thiosemicarbazones under conditions of acid activation of sulfureous nucleophile are spirocyclic furylmethylene-1,3,4-thiadiazolines.

Earlier, we reported that the heterocyclization of α,β-unsaturated cyclanones with thiourea in basic and acidic media lead to the formation of compounds of hydroazine series with an annelic alicyclic fragment.[1,2]

To develop convenient synthesis of condensed and spirocyclic hydroazolic compounds, we investigated reactions of carbonyl substrates of furan series with thiosemicarbazide under various conditions. These heterocyclic derivatives are of potential biological activity and can be used in medicine.[3]



Scheme 1

α,β-Unsaturated cyclic and acyclic ketones **1a–d** were used as substrates. Condensations of enones **1** and thiosemicarbazide were carried out in alcoholic medium, without activation of reagents and with the use of triethylamine as a basic catalyst. The interaction without catalyst leads to corresponding thiosemicarbazones **2** with a yield of up to 84% (Scheme 1).

In the IR spectra of thiosemicarbazones **2**,† there is intense absorption due to valence vibrations associated with primary and secondary thioamide groups at 3460–3230 cm^{-1} (ν NH_2, NH), characterised by three maxima. The signals of protons of thioamidic group are characteristic in the ^{1}H NMR spectrum, which gives separate signals for primary (δ 9.32–10.55 ppm) and secondary (δ 1.8–2.0 ppm) thioamidic groups.

Reaction does not stop at a stage of formation of a linear thiosemicarbazone at longer (12–15 h) heating in the presence

† ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-MSL 400 spectrometer with a working frequency of 400 MHz and 100 MHz, respectively, for solutions of compounds in [$^2H_6$]DMSO, TMS as an internal standard. IR spectra were measured on a FCM-1201 spectrophotometer for samples in KBr tablets. A course of reaction and purity of synthesized compounds were controlled by TLC on Silufol UV-254 plates, in a mixture of hexane, ethyl acetate and chloroform in a 2:2:1 ratio. GC-MS spectra were recorded on a TRACE DSQ instrument.

Thiosemicarbazones **2a–d**. Solution of 0.05 mol of corresponding ketone and 0.06 mol of thiosemicarbazide in 60 ml of Pr^{i}OH was refluxed for 4 h. Then the reaction mixture was cooled and product of reaction was filtered off and recrystallized from isopropanol.

2a: yield 84%; mp 143–145 °C (Pr^{i}OH). IR (ν/cm^{-1}): 3362, 3340 (NH_2), 3220 (NH), 3150–3100 (=CH), 3180–3160 (CH_{Fur}), 2980–2860 (Me), 1605 (C=C), 1200 (C=S). ^{1}H NMR, δ: 1.89 (s, 1H, NH), 2.12 (s, 3H, Me), 6.19 (d, 1H, =CH–C, *J* 6.55 Hz), 6.74 (d, 1H, =CH–Fur, *J* 6.55 Hz), 6.79–6.83 (m, 2H, Fur), 7.29 (d, 1H, Fur), 10.53 (s, 2H, NH_2). MS, *m*/*z* (%): 60.2 (100), 66.2 (22), 94.0 (96), 104.5 (8), 114.8 (54), 149.5 (48), 153.3 (54), 209.2 (30). Found (%): C, 51.55; H, 5.28; N, 20.35. Calc. for $C_9H_{11}N_3OS$ (%): C, 51.65; H, 5.30; N, 20.08.

2b: yield 75%; mp 173–175 °C (Pr^{i}OH). IR (ν/cm^{-1}): 3400, 3300 (NH_2), 3150 (NH), 3100–3000 (=CH), 3170–3150 (CH_{Fur}), 2940–2860 (CH_2), 1600 (C=C), 1200 (C=S). ^{1}H NMR, δ: 1.55 (s 1H, NH), 2.12–2.42 (m, 8H, CH_2), 6.18 (s 1H, =CH–Fur), 6.79–6.86 (m, 2H, Fur), 7.31 (s 1H, Fur), 9.56 (s, 2H, NH_2). ^{13}C NMR, δ: 22.7, 22.9, 23.1, 41.1 (4CH_2), 129.5 (=*C*H–Fur), 115.0 (C^4_{Fur}), 112.4 (C^3_{Fur}), 140.8 (C^2_{Fur}), 148.4 (C^5_{Fur}), 142.8 (=C–), 154.8 (C=N), 184.5 (C=S). Found (%): C, 57.57; H, 6.23; N, 19.97. Calc. for $C_{12}H_{15}N_3OS$ (%): C, 57.81; H, 6.06; N, 19.85.

For characteristics of compounds **2c** (yield 68%) and **2d** (yield 55%), see Online Supplementary Materials.

of catalytic amounts of triethylamine and owing to activation of the nitrous nucleophilic centre gives *N*-thiocarbamoylpyrazolines **3** with yields of up to 45%. Vibrations of primary thioamidic groups are observed in high-frequency area (ν NH_2) in IR spectra of synthesized pyrazolines. In the ^{13}C NMR spectrum, there are signals of β-carbon atom (δ 51.6–53.9 ppm) of synthesized pyrazolines, whereas in that of thiosemicarbazone sp^2-hybridized α,β-carbon atoms of a side chain resound in the area of 115–156 ppm.

Regiospecific heterocyclization of thiosemicarbazones **2**, which led to thiocarbamoylpyrazolines **3**,‡ is confirmed by GC-MS data and spectral characteristics of compounds **3**. The fragmentation of the molecular ion of **3a** led to appearance of the primary fragmentary ion which consists of dehydroazirinic cycle ($C_3H_6N_2S$, *m*/*z* 102.2), that is typical of pyrazolinic systems. Formation of a regioisomeric compound under conditions of *exo*-azaheterocyclization is not observed.

To study the chemical properties of thiosemicarbazones **2a–d**, we investigated their heterocyclization reactions under conditions of acid and basic activation of a reagent.

First, cyclization of thiosemicarbazones **2a–d** was carried out in pyridine in the presence of an acylating agent (acetic anhydride). Analysis of spectral characteristics of obtained products showed that reaction proceeds regioselectivitely owing to intramolecular attack of the sulfureous nucleophilic centre at the carbon atom of azometinic fragment without participation of C=C bond of chalcone, giving 5-furylmethylene-1,3,4-thiadiazolines **4a–d** with yields of up to 82%.§ IR spectra of compounds **4** exhibit bands of valence vibrations of C=C fragment, conjugated with a benzene ring, with a maximum at 1610–1600 cm^{-1}. This absorption band also occurs in initial ketones. ^1H NMR spectra show singlet signals of vinyl protons at δ 5.75–5.79 ppm (the presence of two doublets of vinyl protons at 6.18 and 6.24 ppm, *J* 6.55 Hz, is characteristic of compound **4a**). Signals of quaternary carbon atom at 60.0–85.5 ppm, carbonyl carbon of acyl groups (168.1–170.4 ppm), azomethinic carbon (135.8–142.0 ppm), vinyl carbon of substituents at the 5-position (112.0–113.1 ppm) and sp^2-hybridized carbon of cycloalkane rings (150.1–153.0 ppm) are observed in ^{13}C NMR spectra.

Under basic catalysis conditions, azacyclization leads to formation of *N*-thiocarbamoylpyrazolines **3** with yields of up to 91%. Physicochemical and spectral characteristics of pyrazolines coincide with those obtained by condensation of enones with thiosemicarbazide.

Thus, the interaction of furfurylidene ketones with thiosemicarbazide under the influence of temperature depending on conditions can proceed regiodirectively to afford corresponding thiosemicarbazones or furyl substituted thiocarbamoylpyrazolines.

Heterocyclization of thiosemicarbazones of furan chalcones **2a–d** under conditions of acylation proceeds regioselectively to give 5-furfurylidene-1,3,4-thiadiazolines, including spirocyclic ones. The use of basic catalysis for heterocyclization of **2a–d** allows one to carry out regiodirected synthesis of *N*-thiocarbamoylpyrazolines.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.01.021.

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Received: 10th July 2008; Com. 08/3175

‡ *Synthesis of* N-*thiocarbamoylpyrazolines* **3a–d**.

Procedure I. Solution of 0.06 mol of corresponding ketone and 0.06 mol of thiosemicarbazide in 60 ml of isopropanol, was refluxed for 15 h in the presence of 0.12 mol of triethylamine. Then the reaction mixture was added to 5% water solution of HCl. The product was filtered off and recrystallized from isopropanol.

Procedure II. Solution of 0.05 mol of corresponding thiosemicarbazone in 45 ml of isopropanol was refluxed for 4 h in the presence of 0.10 mol of triethylamine. Then, the reaction mixture was treated analogously to procedure I.

3a: yield 51% (procedure I), 85% (procedure II); mp 186–188 °C (Pr^iOH). IR (ν/cm^{-1}): 3331, 3325 (NH_2), 3115–3025 (=CH), 1607 (C=N), 1189 (C=S), 760, 825 (=CH). ^1H NMR, δ: 2.21 (s, 3H, Me), 2.31–2.59 (d, 2H, CH_2), 3.21 (t, 1H, CH–N), 6.41–6.79 (m, 2H, Fur), 7.56 (d, 1H, Fur), 10.24 (s, 2H, NH_2). ^{13}C NMR, δ: 19.9 (Me), 38.4 (CH), 53.6 (C–N), 107.9 (C^4_{Fur}), 111.0 (C^3_{Fur}), 143.5 (C^2_{Fur}), 148.9 (C^5_{Fur}), 154.3 (Me–C=N), 177.8 (NH_2–C=S). MS, *m*/*z* (%): 91.2 (40), 102.2 (100), 106.4 (12), 119.0 (10), 134.2 (12), 149.6 (25), 209.2 (10). Found (%): C, 51.77; H, 5.55; N, 20.23. Calc. for $C_9H_{11}N_3OS$ (%): C, 51.65; H, 5.30; N, 20.08.

3b: yield 45% (procedure I), 75% (procedure II); mp 182–185 °C (Pr^iOH). IR (ν/cm^{-1}): 3408, 3395 (NH_2), 3108 (=CH), 2960–2830 (CH_2, CH), 1690 (C=N), 1190 (C=S). ^1H NMR, δ: 1.20–2.10 (m, 8H, CH_2), 2.08 (s, 1H, CH), 4.10 (s, 1H, CH–N), 6.06–6.35 (m, 2H, Fur), 7.37 (d, 1H, Fur), 9.56 (s, 2H, NH_2). ^{13}C NMR, δ: 22.6, 24.1, 25.4, 31.4 ($4CH_2$), 43.5 (CH), 53.9 (C–N), 105.0 (C^4_{Fur}), 105.4 (C^3_{Fur}), 141.8 (C^2_{Fur}), 149.4 (C^5_{Fur}), 150.4 (C=N), 175.5 (C=S). Found (%): C, 57.94; H, 6.21; N, 16.79. Calc. for $C_{12}H_{15}N_3OS$ (%): C, 57.81; H, 6.06; N, 16.85.

3c: yield 46% (procedure I), 86% (procedure II); mp 193–194 °C (Pr^iOH). IR (ν/cm^{-1}): 3311, 3309 (NH_2), 3100–3020 (=CH), 2880 (CH_2, CH), 1600 (C=N), 1200 (C=S). ^1H NMR, δ: 1.32–1.94 (m, 6H, CH_2), 2.11 (s, 1H, CH), 6.25 (s, 1H, CH–N), 6.45–6.53 (m, 2H, Fur), 7.37 (d, 1H, Fur), 9.31 (s, 2H, NH_2). ^{13}C NMR, δ: 23.3, 25.4, 25.4, ($3CH_2$), 45.8 (CH), 53.5 (C–N), 105.2 (C^4_{Fur}), 110.9 (C^3_{Fur}), 142.7 (C^2_{Fur}), 150.4 (C^5_{Fur}), 160.1 (C=N), 175.8 (C=S). Found (%): C, 56.25; H, 5.57; N, 17.69. Calc. for $C_{11}H_{13}N_3OS$ (%): C, 56.15; H, 5.57; N, 17.86.

For characteristics of **3d**, see Online Supplementary Materials.

§ *Synthesis of 1,3,4-thiadiazolines* **4a–d**. Solution of 0.015 mol of corresponding thiosemicarbazone and 0.03 mol of acetic anhydride in 30 ml of pyridine was stirred for 4 h. Then the solvent was evaporated *in vacuo*. The obtained precipitate was washed with ethanol and recrystallized from ethanol.

4a: yield 63%; mp 160–162 °C (EtOH). IR (ν/cm^{-1}): 3150 (NH), 1690 (Amide I), 1610 (C=N), 1520 (Amide II), 1625 (C=C). ^1H NMR, δ: 1.52 (s, 3H, COMe), 2.15 (s, 3H, COMe), 2.21 (s, 3H, Me), 6.20 (d, 1H, =CH–C, *J* 6.55 Hz), 6.63 (d, 1H, HC=C, *J* 6.55 Hz), 6.67–6.89 (m, 2H, β-Fur), 7.32 (d, 1H, α-Fur), 9.6 (s, 1H, NH). Found (%): C, 53.10; H, 5.50; N, 13.96. Calc. for $C_{13}H_{15}N_3O_3S$ (%): C, 53.61; H, 5.15; N, 14.34.

4b: yield 62%; mp 187–190 °C (EtOH). IR (ν/cm^{-1}): 3140 (NH), 1680 (Amide I), 1615 (C=N), 1540 (Amide II), 1630 (C=C). ^1H NMR, δ: 1.22–2.32 (m, 8H, CH_2), 1.92 (s, 3H, COMe), 2.45 (s, 3H, COMe), 5.8 (s, 1H, HC=C), 6.71–6.82 (m, 2H, β-Fur), 7.32 (d, 1H, α-Fur), 8.29 (s, 1H, NH). ^{13}C NMR, δ: 26.8, 28.7, 31.4, 56.2 ($4CH_2$), 85.1 (C_{spiro}), 36.3 (Me), 38.2 (Me), 129.5 (=CH–Fur), 128.1 (C^4_{Fur}), 114.5 (C^3_{Fur}), 111.5 (C^2_{Fur}), 149.1 (C^5_{Fur}), 142.1 (C=N), 144.1 (=C–C), 178.9 (C=O), 179.8 (C=O). Found (%): C, 57.35; H, 5.63; N, 12.60. Calc. for $C_{16}H_{19}N_3O_3S$ (%): C, 57.69; H, 5.74; N, 12.60.

4c: yield 59%; mp 167–169 °C (EtOH). IR (ν/cm^{-1}): 3390 (NH), 1680 (Amide I), 1600 (C=N), 1500 (Amide II), 1633 (C=C). ^1H NMR, δ: 1.22–1.72 (m, 6H, CH_2), 1.52 (s, 3H, COMe), 2.15 (s, 3H, COMe), 6.1 (s, 1H, HC=C), 6.72–6.82 (m, 2H, β-Fur), 7.29 (d, 1H, α-Fur), 8.8 (s 1H, NH). ^{13}C NMR, δ: 27.9, 30.3, 59.2 ($3CH_2$), 83.2 (C_{spiro}), 39.3 (Me), 44.2 (Me), 129.1 (=CH–Fur), 128.3 (C^4_{Fur}), 114.9 (C^3_{Fur}), 141.2 (C^2_{Fur}), 149.7 (C^5_{Fur}), 141.9 (C=N), 150.6 (=C–), 173.9 (C=O), 179.1 (C=O). Found (%): C, 56.44; H, 5.37; N, 13.96. Calc. for $C_{15}H_{17}N_3O_3S$ (%): C, 56.41; H, 5.37; N, 13.16.

For characteristics of **4d**, see Online Supplementary Materials.