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SYNTHESIS OF THE THIOAMIDE DERIVATIVES OF METHYL VINYL KETONE AND THEIR CYCLIZATION TO 2,3-DIHYDRO-4H-THIOPYRAN-4-ONES

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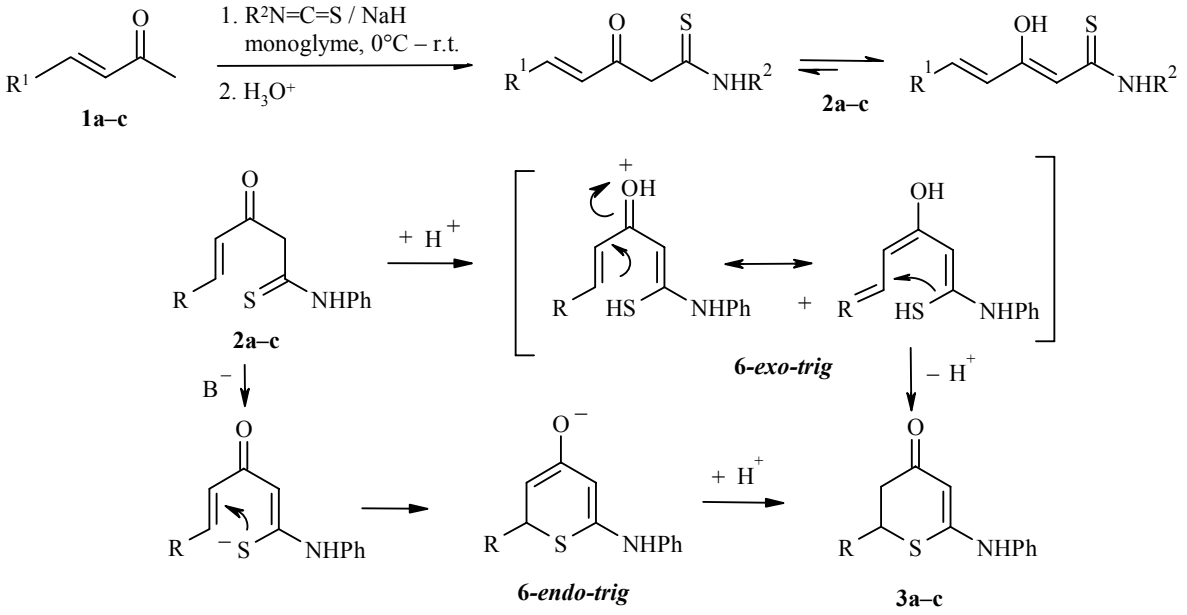
A novel synthesis of thioamide derivatives of methyl vinyl ketone and their cyclization to 2,3-dihydro-4H-thiopyran-4-ones were developed.

Keywords: benzylideneacetone, 2,3-dihydro-4H-thiopyran-4-ones, α-ionone, pseudoionone phenyl isothiocyanate, thioamides.

The structure of many organic compounds of type **1**, including natural products, incorporates the methyl vinyl ketone fragment. We have developed a simple method which makes it possible to build a thioamide function on the methyl group of such compounds. It consists in the reaction of the anion generated *in situ* from arylidene- or alkylideneacetone **1**, in particular, benzylidene- acetone, α-ionone, and pseudoionone, with an isothiocyanate. Both aromatic and aliphatic isothiocyanates are reactive under the applied reaction conditions (from 0°C to room temperature). In contrast to the earlier report [1], the reaction yields linear thioamides which proved to be versatile synthons to give heterocyclic compounds in intra- and intermolecular reactions [2].



2,3 a R = Ph, **b** R = 2,6,6-trimethylcyclohex-2-enyl, **c** CH_2=$CMe(CH_2)_3MeC$=CH–

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Now we present the cyclization reactions converting the prepared thioamides **2a-c** into the derivatives of 2,3-dihydro-4H-thiopyran-4-one **3a-c**. With reference to the Baldwin rules [3] they can proceed in an alkaline medium as a 6-*endo-trig,* and in an acidic medium as a 6-*exo-trig* process, although the former seems to be disfavored. In the presence of triethylamine, prolonged heating of the thioamides in ethanol secures only a moderate yield of **3**. When thioamides **2** are heated in toluene or benzene with TsOH acid, thiopyranones **3** are formed along with some difficultly identifiable and removable by-products. However, if the BF_3–AcOH complex is used as the reaction catalyst, a quantitative yield (crude product) of thiopyranones **3** is reached in 10 min.

Both thioamides **2** and their cyclic counterparts turned out to be highly reactive substrates in other reactions, the results of which will be published separately.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a Bruker DPX 400 spectrometer (400 and 100 MHz for ^1H and ^{13}C respectively). For 2D-spectra a standard Bruker software was used. IR spectra were taken with a Specord M-80 instrument.

Thioamides 2a-c (General Procedure). A solution of the appropriate benzylidene- or alkylideneacetone (10 mmol) and phenyl isothiocyanate 1.65 g (12 mmol) in 10 ml of monoglyme was added dropwise under nitrogen to a stirred cold (0°C) suspension of NaH (25 mmol, 80% in mineral oil) in 25 ml of monoglyme. The reaction mixture was allowed to reach room temperature and stirred for 2.5 h or left standing overnight. The yellow-brown mixture was poured into a 10% HCl solution with crushed ice and the organic product was extracted with ethyl acetate. After a routine work-up, the crude products were chromatographed on silica gel using *n*-hexane–ethyl acetate (1:1) as the eluent. Recrystallization from appropriate solvent gave the final products.

3,4-Dihydrothiopyran-4-ones 3a-c (General Procedure). Two ml of BF_3–2AcOH (36% BF_3, Fluka) were added to a stirred solution of the thioamide **2** (0.33 mmol) in 2 ml of dry THF and the reaction was monitored by TLC until the substrates disappeared. Upon dilution with water, the organic product was extracted with ethyl acetate and the extract was washed with water and passed under reduced pressure through a 10-cm column packed with Al_2O_3. Concentration of the eluate gave crude products which were purified by recrystallization from toluene. In the case of **3c**, the crude product was chromatographed on silica gel using *n*-hexane–ethyl acetate (1:1) as the eluent.

3-Hydroxy-5-phenylpenta-2,4-dienethioic acid phenylamide (2a). Yield 86%. Yellow solid; mp 140-143°C (methanol). IR spectrum (KBr), ν_{max}, cm^{-1}: 3292 (NH), 1630 (C=C, CH), 1522 (NH, CN), 1400 (OH, CO), 1318 (CN), 1208 (NCS). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz), *enol form*: 6.00 (1H, s, CH=COH); 6.75 (1H, d, *J* = 15.8, PhCH=C<u>H</u>); 7.32-7.77 (10H, m, $2C_6H_5$); 7.61 (1H, d, *J* = 7.6, PhC<u>H</u>=CH); 11.40 (1H, s, NH), 14.26 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 103.90 (<u>C</u>HCOH), 124.68, 128.26, 129.10, 129.35, 135.71, 138.82 (C_6H_5), 129.83 (PhCH=<u>C</u>H), 135.88 (Ph<u>C</u>H=CH), 167.04 (C–OH), 189.72 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz), *ketone form*: 4.30 (2H, s, $COCH_2CS$); 6.99 (1H, d, *J* = 16.2, PhCH=C<u>H</u>); 7.32-7.77 (10H, m, 2 C_6H_5); 7.86 (1H, d, *J* = 7.7, PhC<u>H</u>=CH); 11.80 (1H, s, NH). Found, %: C 72.11; H 5.23; N 4.95; S 11.72. $C_{17}H_{15}NOS$. Calculated, %: C 72.57; H 5.37; N 4.98; S 11.40.

3-Hydroxy-5-(2,6,6-trimethylcyclohex-2-enyl)penta-2,4-dienethioic Acid Phenylamide (2b). Yield 61%. Yellow solid**;** mp 125-127°C (hexane–benzene). IR spectrum, ν_{max}, cm^{-1}: 3304 (NH), 2970-2880 (OH···S=C, C–H), 1642 (C=C, C–H), 1586 (C=C), 1526 (NH, C–N), 1400 (OH, C–O), 1322 (C–N), 1208 (NCS). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz), *enol form*: 0.80 (3H, s, CH_3); 0.88 (3H, s, CH_3); 1.10-1.23 (1H, m, =CHCH_2C<u>H</u>H); 1.30-1.43 (1H, m, =CHCH_2CH<u>H</u>); 1.5 (3H, s, CH_3); 1.94-2.03 (2H, m, =CHC<u>H</u>$_2$CHH); 2.3 (1H, d, *J* = 9.6, C<u>H</u>CH=CH); 5.46 (1H, s, C=C<u>H</u>CH_2); 5.81 (1H, s, C<u>H</u>=COH); 5.90 (1H, d,

J = 15.2, C=C<u>H</u>COH); 6.37 (1H, dd, J = 15.2, J = 9.9, CHC<u>H</u>=CH); 7.30-7.52 (3H, m, C_6H_5); 7.58 (2H, d, J = 7.8, C_6H_5); 11.25 (1H, s, NH), 14.11 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.87 (CH_3), 23.00 (=CCH_2), 26.95 (CH_3), 27.04 (CH_3), 31.33 ($CHCH_2\underline{C}H_2$), 32.58 ($CH_2CH_2\underline{C}$), 53.98 (<u>C</u>HCH=CH), 102.29 (<u>C</u>H=COH), 122.11 (CH=<u>C</u>HCH$_2$), 128.36 (CH=<u>C</u>HCOH), 131.17 (<u>C</u>H=CHCOH), 132.93 ($CH_3\underline{C}$=CH), 124.54, 126.55, 129.01, 138.79 (C_6H_5), 166.73 (COH), 189.97 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz), *ketone form*: 0.84 (3H, s, CH_3); 0.87 (3H, s, CH_3); 1.10-1.23 (1H, m, =CHCH$_2$C<u>H</u>H); 1.30-1.43 (1H, m, =CHCH$_2$CH<u>H</u>); 1.49 (3H, s, CH_3); 1.94-2.03 (2H, m, =CHC<u>H</u>$_2$CHH); 2.34 (1H, d, J = 9.6, C<u>H</u>CH=CH); 4.20 (2H, s, CSCH$_2$CO); 5.46 (1H, s, C=C<u>H</u>CH$_2$); 6.13 (1H, d, J = 15.8, C=C<u>H</u>CO); 6.71 (1H, dd, J = 15.8, J = 9.9, CHC<u>H</u>=CH); 7.30-7.52 (3H, m, C_6H_5); 7.81 (2H, d, J = 7.8, C_6H_5); 11.76 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.87 (CH_3), 23.08 (=CCH_2), 26.77 (CH_3), 27.94 (CH_3), 31.14 (=$CHCH_2\underline{C}H_2$), 32.86 ($CH_2CH_2\underline{C}$), 53.89 (<u>C</u>HCH=CH), 58.72 (CH_2CS), 122.70 (C=<u>C</u>HCH$_2$), 132.19 ($CH_3\underline{C}$=CH), 139.83 (CH=<u>C</u>HCO), 123.27, 126.55, 129.08, 140.48 (C_6H_5), 149.34 (<u>C</u>H=CHCO), 193.63 (C=O), 195.14 (C=S). Found, %: C 73.03; H 7.45; N 4.15; S 10.16. $C_{20}H_{25}NOS$. Calculated, %: C 73.35; H 7.96; N 4.28; S 9.79.

3-Hydroxy-7,11-dimethyldodeca-2,4,6,10-tetraenethioic Acid Phenylamide (2c). Yield 65%. Dark oil. IR spectrum (thin layer), ν_{max}, cm^{-1}: 3276-3164 (NH, OH), 1738 (C=O), 1612-1556 (C=C–OH, C=C), 1060 (C=S). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz), *enol form*: 1.86 (6H, s, CH_3); 2.02 (3H, s, CH_3); 2.08-2.25 (4H, m, 2CH_2); 4.94-5.04 (1H, m, =C<u>H</u>CH$_2$); 5.60 (1H, s, C<u>H</u>COH); 5.73 (1H, d, J =14.6, =C<u>H</u>COH); 5.94 (1H, d, J = 11.3, =C<u>H</u>CH=); 7.14-7.36 (8H, m, C_6H_5, =CHC<u>H</u>=CH); 7.39-7.49 (4H, m, C_6H_5); 8.12 (1H, br. s, NH), 14.57 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.47 (CH_3), 17.71 (CH_3), 25.70 (CH_3), 26.39 (CH<u>C</u>H$_2$CH$_2$), 40.42 (CH$_2$<u>C</u>H$_2$C), 103.80 (C=COH), 120.48 (=CHCH=), 123.02 (<u>C</u>HCOH), 123.74 (C=<u>C</u>HCH$_2$), 132.58 (<u>C</u>=CHCH$_2$), 123.38, 125.33, 126.81, 137.89 (C_6H_5), 141.03 (CH_3CCH$_2$), 142.90 (<u>C</u>=CHCOH), 171.20 (C–OH), 197.13 (C=S). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz), *ketone form*: 1.88 (6H, s, CH_3); 2.02 (3H, s, CH_3); 2.08-2.25 (4H, m, 2CH_2); 4.24 (2H, s, CH_2CS); 5.04-5.16 (1H, m, =C<u>H</u>CH$_2$); 6.07 (1H, d, J = 11.3, =C<u>H</u>CH=); 6.15 (1H, d, J =14.9, =C<u>H</u>COH); 7.14-7.36 (8H, m, C_6H_5, =CHC<u>H</u>=CH); 7.39-7.49 (4H, m, C_6H_5); 11.21 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.71 (CH_3), 21.06 (CH_3), 25.70 (CH_3), 26.95 (CH<u>C</u>H$_2$CH$_2$), 40.66 (CH$_2$<u>C</u>H$_2$C), 60.42 (<u>C</u>H$_2$CS), 121.86 (=CHCH=), 124.25 (<u>C</u>HCO), 132.17 (<u>C</u>=CHCH$_2$), 123.48, 125.11, 126.50, 138.73 (C_6H_5), 155.26 (<u>C</u>=CHCOH), 190.54 (C=S), 193.55 (C=O). Found, %: C 73.23; H 7.65; N 4.13; S 10.08. $C_{20}H_{25}NOS$. Calculated, %: C 73.35; H 7.69; N 4.28; S 9.79.

2-Phenyl-6-phenylamino-2,3-dihydrothiopyran-4-one (3a). Yield 54%. Pale yellow solid; mp 195-197°C (toluene). IR spectrum (KBr), ν_{max}, cm^{-1}: 3212 (NH), 1590 (C=O, C=C), 1550-1500 (NH, C–N, C=C), 1444 (C–H), 1262 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.65 (1H, dd, J = 16.2, J = 2.8, C<u>H</u>H); 3.02 (1H, dd, J = 16.1, J = 3.0, CH<u>H</u>); 4.77 (1H, dd, J = 12.7, J = 2.5, Ph–C<u>H</u>); 5.67 (1H, s, =CH); 7.10 (1H, t, J = 7.3, N–Ph); 7.19 (2H, d, J = 8.0, N–C_6H_5); 7.26-7.40 (5H, m, C–C_6H_5, N–C_6H_5); 7.45 (2H, d, J = 7.5, C–C_6H_5); 9.41 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 44.38 (CH_2), 45.03 (CH), 98.55 (=CH), 123.53, 125.13, 128.12, 128.58, 129.18, 129.53, 138.76, 139.33 (2 C_6H_5), 160.92 (=C), 192.20 (C=O). Found, %: C 72.49; H 5.29; N 4.89; S 11.20. $C_{17}H_{15}NOS$. Calculated, %: C 72.57; H 5.37; N 4.98; S 11.40.

6-Phenylamino-2-(2,6,6-trimethylcyclohex-2-enyl)-2,3-dihydrothiopyran-4-one (3b). Yield 90%. Pale yellow solid; mp 193-197°C (heptane–toluene). IR spectrum ($CHCl_3$), ν_{max}, cm^{-1}: 3400 (NH), 1608 (C=O, C=C), 1550-1500 (NH, C–N, C=C), 1252 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 0.84 (3H, s, CH_3); 0.95 (3H, s, CH_3); 1.12-1.17 (1H, m, CC<u>H</u>HCH$_2$); 1.56 (1H, dd, J = 22.4, J = 9.3, CCH<u>H</u>CH$_2$); 1.69 (1H, s, CC<u>H</u>C); 1.81 (3H, s, CH_3); 1.97 (2H, s, =CCH_2); 2.53 (1H, t, J = 15.8, COC<u>H</u>H); 2.87 (1H, t, J = 15.6, COCH<u>H</u>); 3.80 (1H, d, J = 14.1, SCH); 5.48 (1H, s, C=C<u>H</u>CH$_2$); 5.72 (1H, s, C=CHCO); 7.05-7.10 (3H, m, C_6H_5); 7.11-7.27 (2H, m, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.27 (=C<u>C</u>H$_2$), 26.37 (CH_3), 27.08 (CH_3), 28.41 (CH_3), 30.38 (=$CCH_2\underline{C}H_2$), 33.27 ($CH_2\underline{C}$), 43.53 (SCH), 47.89 (CH_2CO), 53.46 (=C<u>C</u>H), 99.62 (C<u>C</u>HCO), 123.34, 125.51, 129.45, 138.30 (C_6H_5), 124.76 (=<u>C</u>CH$_2$), 132.29 (<u>C</u>=CCH$_2$), 162.35 (S<u>C</u>=CH), 195.33 (C=O). Found, %: C 73.33; H 7.48; N 4.20; S 9.65. $C_{20}H_{25}NOS$. Calculated, %: C 73.35; H 7.69; N 4.28; S 9.79.

2-(2,6-Dimethylhepta-1,5-dienyl)-6-phenylamino-2,3-dihydrothiopyran-4-one (3c). Yield 52%. Dark oil. IR spectrum (thin layer), ν_{max}, cm^{-1}: 3188 (NH), 1738 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.52 (3H, s, CH_3); 1.61 (3H, s, CH_3); 1.97 (3H, s, CH_3); 1.88-2.06 (4H, m, $2CH_2$); 2.58 (2H, t, *J* = 7.2, CH_2CO); 4.01-4.08 (1H, m, CHS); 4.95-5.06 (1H, m, C<u>H</u>CH_2); 5.46-5.53 (1H, m, =C<u>H</u>CH); 5.75 (1H, s, CHCO); 7.05-7.13 (3H, m, C_6H_5); 7.23-7.28 (2H, m, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2 (CH_3), 17.77 (CH_3), 21.08 (CH_3), 25.70 (SCH), 25.73 (=C<u>C</u>H_2), 39.38 (<u>C</u>H_2C=), 46.80 (<u>C</u>H_2CO), 99.57 (=<u>C</u>HCO), 120.80 (=<u>C</u>HCHS), 123.22 (=CCH_2CH_2), 123.37, 125.50, 129.45, 138.02 (C_6H_5), 132.54 (CH_3<u>C</u>=CH), 142.35 (CH_2CH_2<u>C</u>=C), 161.90 (C–NH), 194.18 (C=O). Found, %: C 73.29; H 7.55; N 4.22; S 10.01. $C_{20}H_{25}NOS$. Calculated, %: C 73.35; H 7.69; N 4.28; S 9.79.

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