Synthesis of 5,6-Dihydro-4*H*-thiopyran-4-ones

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The anions of 1,4-diaryl-3-buten-2-ones **1** reacts with arylisothiocyanates, yielding intermediates **4** which can ring close to 5,6-dihydro-4*H*-thiopyran-4-ones **5**. Under similar reaction conditions ethyl 3-oxo-4-pentenoates **7** gives the 6-spiropyrans **9**. Methylation of **3** gives the *S*-methylated open form **6**.

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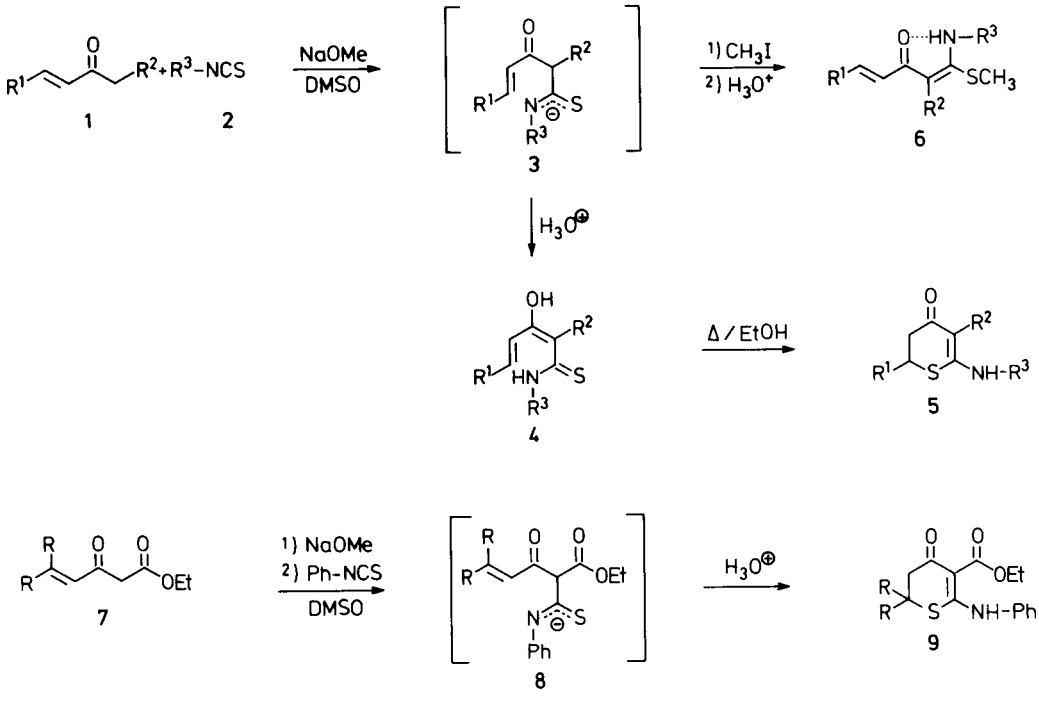
In a previous paper [1] we described the reactin of various 1-buten-3-one enolates with aromatic isothiocyanates giving 3-substituted 6-aryl-2-arylamino-5,6-dihydro-4*H*-thiopyran-4-ones in fair yields. In this reaction an intermediate anion was postulated, which, after acidification, undergoes an intramolecular Michael-type addition yielding the thiopyran. It was also shown that the intermediate, after reaction with methyl iodide, gives the 2,3-dihydro-6-methylthio-4(1*H*)-pyridones, the Michael-addition now taking place at the NH function. Augustin [2] has described the possiblity of ring opening of 5,6-dihydro-4*H*-thiopyran-4-ones with sodium hydride, whereupon subsequent methylation gives the pyridines. Schweiger [3] has reported an interesting rearrangement of a 6,6-dimethylthiopyran with base leading to a 5,6-dihydropyridinethione.

Scheme



1 2 3 4 5 6 7 8 9

Compound	R_1	R_2	R_3
5a	C_6H_5	C_6H_5	C_6H_5
5b	C_6H_5	C_6H_5	2-CH_3-C_6H_4
5c	C_6H_5	C_6H_5	4-Br-C_6H_4
5d	4-Cl-C_6H_4	C_6H_5	2-$CH_3C_6H_4$
5e	C_6H_5	4-CH_3O-C_6H_4	C_6H_5
6a	C_6H_5	C_6H_5	C_6H_5
6b	4-CH_3-C_6H_4	C_6H_5	C_6H_5

Compound	R
9a	$-CH_3$
9b	$-CH_2-CH_2-CH_2-CH_2-$
9c	$-CH_2-CH_2-CH_2-CH_2-CH_2-$

These results have prompted us to investigate related reactions of anions of activated methylene compounds with isothiocyanates in a dipolar aprotic solvent (dimethyl sulfoxide), with the aim of preparing new thiopyranes including spiro-thiopyranes. The anions of the easily accessible styryl benzyl ketones **1** [4] dissolved in anhydrous dimethyl sulfoxide, react with arylisothiocyanates, giving 5,6-dihydro-4*H*-thiopyran-4-ones **5** in fair yields.

In the case of ketones **1** the crude reaction product consists mostly of the acyclic intermediates **4**, which, after refluxing in ethanol for some hours, ring close to the thiopyrans **5**. Synthesis of the 3-oxo-4-pentenoates **7** which appeared to be promising starting materials has been described by Bodalski *et al.* [5]. We have found that the red enolates of compounds **7** reacts readily with arylisothiocyanates yielding the 6-spiropyrans **9**. Reaction of enolates of **1** or **7** with aliphatic isothiocyanates such as benzyl isothiocyanate, only showed small amounts of the desired product.

Base-catalysed rearrangement of the non aromatic 2-arylamino-4*H*-thiopyran-4-ones to the corresponding pyridines, as described by Augustin [2] or Schweiger [3] for related systems, does not take place in the present series of compounds **5** and **9**, even prolonged heating of compounds **9** in a mixture of dimethyl formamide/sodiumhydride only resulted in isolation of starting materials, probably suggesting that steric hindrance prevent formation of a pyridine ring.

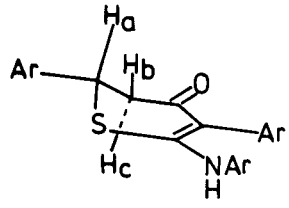
The intermediate anion **3** reacted with methyl iodide to give orange crystals of **6**. However it was not possible to cyclize compounds **6** to the related dihydropyridones [1], by heating compounds **6** in ethanol. Corresponding methylation of intermediate **8** was unsuccessful.

The structures of thiopyranones **5** and **9** were assigned on the basis of spectroscopic and analytic data. The existence of NH groups in spiro compounds **9**, was revealed by recording the proton-coupled ^{15}N-nmr spectra obtained by use of the INEPT pulse sequence with nitromethane as a reference. All the ^{15}N-nmr spectra showed a doublet due to the one bond NH coupling $\simeq$ 91 Hz Table 1. These results were supported by the ir data, having a sharp line at 3360 cm^{-1} in compounds **5** (NH stretch) or 3440 cm^{-1} in compounds **9**. Carbonyl stretching line are seen at 1620 cm^{-1} in **5** or at 1640 cm^{-1} in **9**. The ^{1}H-nmr spectra also show a broad peak from the NH proton at 6.5 ppm **5** or 12.1 ppm **9**, in both cases exchangeable with deuterium oxide. The ^{1}H-nmr spectra of compound **5** contain an ABX pattern [6] due to the coupling between H_a, H_b and H_c.

Table 1

^{15}N-NMR Coupling Constants for Spiro Compounds **9**

Compound	J_{NH} doublets in Hz
9a	90.66
9b	93.99
9c	91.66



Thiopyranones of type **5** were all found to have approximately the same shifts values for H_a, H_b and H_c at δ = 4.7 (H_a), 3.2 (H_b), and 3.0 ppm (H_c), and coupling constants J_{ab} = 3.0 Hz J_{bc} = 16.5 Hz and J_{ac} = 13.5 Hz corresponding well to the depicted structure.

Likewise structures of the acyclic methylated compounds **6** were deduced from the ^{1}H-nmr spectra which show a broad peak at 14.3 ppm arising from NH proton, exchangeable with deuterium oxide, and the vinylic protons at 6.5 and 7.6 ppm with a typical *trans* coupling constant (J = 16 Hz). The ir spectra show no NH stretching line, but a sharp line at 1630 cm^{-1} due to the carbonyl group. These data support the structure **6** with the presence of an intramolecular hydrogen bond as shown in the Scheme.

EXPERIMENTAL

Microanalyses were carried out at NOVO A/S, Bagsvaerd, DK. The ^{1}H-nmr spectra were recorded on a Jeol FX 60 Q (**6a-b, 9a-c**) or Bruker AC 250 (**5a-g**). The ^{13}C-nmr spectra were recorded on a Joel FX 60 Q (**5a-g, 6a-b**) or Bruker AC 250 (**9a-c**). The ^{15}N-nmr spectra were recorded on a Bruker AC 250. Ir spectra on a Perkin-Elmer 580 (potassium bromide used in all cases), uv spectra on a Varian CARY 219 (absolute ethanol as solvent in all cases) and Mass spectra on a Varian MAT 311 A. Melting point were obtained on a Büchi - apparatus (uncorrected).

All the required ketones of type **1** and **7** were obtained by known methods [4,5].

Synthesis of 2-Arylamino-5,6-dihydro-4*H*-thiopyran-4-ones.

Method A.

The appropriate ketone **1** (10 mmoles) was suspended in anhydrous dimethylsulfoxide (25 ml). A solution of 232 mg sodium dissolved in 3.7 ml of dry methanol was added, and the mixture stirred for 30 minutes at room temperature. Arylisothiocyanate (10 mmoles) was dropped to the reaction mixture, and the stirring continued for 2 hours at 42°. The resulting mixture was poured into cold water (450 ml, 0°) with stirring, and treated with 1 molar hydrochloric acid (to *p*H = 1-2). The precipitated compound was isolated, washed with water, dried, and refluxed in ethanol.

Method B.

The ketone **7** (12.4 mmoles) was suspended in 25 ml of dry dimethylsulfoxide. 285 mg of sodium dissolved in 4 ml of dry methanol, was added with stirring at room temperature. One equivalent of phenylisothiocyanate (12.6 mmoles) was added to the red solution, and the reaction heated for ½ hour at 40° and then 1 hour at 80°. The reaction mixture was cooled, and poured into 100 ml of cold water with stirring, and treated with 1 molar hydrochloric acid (to *p*H = 2). The water mixture was extracted with chloroform (4 x 30 ml) dried with magnesium sulphate, filtered and evaporated *in vacuo*.

2-Anilino-5,6-dihydro-3,6-diphenyl-4*H*-thiopyran-4-one, **5a**.

Method A gave a yellow compound. Heating in ethanol (50 ml) for 4 hours, followed by cooling and filtering, the thiopyran **5a** was obtained in a yield of 2.1 g (58%), mp 137-140°; ir: 1620 (C=O) 3360 cm^{-1} (NH); uv: λ max (log ε) = 333 nm (4.28); ^{1}H-nmr (deuteriochloroform/TMS): δ = 3.0 (H_c), 3.2 (H_b), 4.7 (H_a), 6.5 (broad, 1H, NH), 7.1-7.6 ppm (m, 15H, aryl); ^{13}C-nmr (deuteriochloroform/TMS): δ = 44.90 (C_5 or C_6), 45.35 (C_5 or C_6), 113.38 (C_3), 125-138 (aryl), 159.49 (C_2), 190.47 ppm (C_4); ms: (relative intensity, %) 357 (100), 252 (51), 131 (70), 103 (37), 89 (25), 77 (42).

Anal. Calcd. for $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92. Found: C, 77.71; H, 5.38; N, 3.81.

5,6-Dihydro-3,6-diphenyl-2-(2-methylanilino)-4*H*-thiopyran-4-one, **5b**.

Method A gave a yellow compound. The crude product was refluxed in ethanol for 4 hours, and the thiopyran **5b** was isolated from the hot suspension; recrystallized from toluene, yield 1.9 g (51%), mp 220-222°; ir: 1615 (C=O) 3360 cm^{-1} (NH); uv: λ max (log ε) = 327 nm (4.27); ^{1}H-nmr (deuteriochloroform/TMS): δ = 2.2 (s, 3H, CH_3), 3.0 (H_c), 3.2 (H_b), 4.7 (H_a), 6.2 (broad, 1H, NH), 7.1-7.6 ppm (m, 14H, aryl): ^{13}C-nmr (deuteriochloroform/TMS): δ = 17.87 (CH_3), 44.91 (C_5 or C_6), 45.41 (C_5 or C_6), 112.60 (C_3), 126-138 (aryl), 160.69 (C_2), 190.08 ppm (C_4); ms: (relative intensity, %) 371 (100), 266 (66), 134 (45), 118 (48), 91 (39).

Anal. Calcd. for $C_{24}H_{21}NOS$: C, 77.59; H, 5.70; N, 3.77. Found: C, 77.64; H, 5.79; N, 3.59.

2-(4-Bromoanilino)-5,6-dihydro-3,6-diphenyl-4*H*-thiopyran-4-one, **5c**.

Method A gave a yellow compound. After reflux in ethanol for 20 hours, compound **5c** was precipitated in the hot solution as white crystals. This compound was recrystallized from toluene, yield 1.35 g (31%), mp 206-208°; ir: 1622 (C=O) 3360 cm^{-1} (NH); uv: λ max (log ε) = 334 nm (4.34); ^{1}H-nmr (deuteriochloroform/TMS): δ = 3.0 (H_c), 3.2 (H_b), 4.7 (H_a), 6.4 (broad, 1H, NH), 7.0-7.6 ppm (m, 14H, aryl); ^{13}C-nmr (deuteriochloroform/TMS): δ = 44.87 (C_5 or C_6), 45.36 (C_5 or C_6), 114.13 (C_3), 126-138 (aryl), 158.08 (C_2), 190.63 ppm (C_3); ms: relative intensity, %) 437 (100), 435 (99), 332 (40), 161 (54), 133 (58), 89 (54).

Anal. Calcd. for $C_{23}H_{18}BrNOS$: C, 63.31; H, 4.16; N, 3.21. Found: C, 63.34; H, 4.21; N, 3.11.

6-(4-Chlorophenyl)-5,6-dihydro-2-(2-methylanilino)-3-phenyl-4*H*-thiopyran-4-one, **5d**.

Method A gave a yellow compound. Reflux of the crude product in ethanol for 4 hours gave a white compound, which was recrystallized from toluene, yield 1.7 g (42%); mp 201-202°; ir: 1620 (C=O) 3360 cm^{-1} (NH); uv: λ max (log ε) = 327 nm (4.22); ^{1}H-nmr (deuteriochloroform/TMS): δ = 3.0 (H_c), 3.2 (H_b), 4.7 (H_a), 6.2 (broad, 1H, NH), 7.1-7.5 ppm (m, 13H, aryl); ^{13}C-nmr (deuteriochloroform/TMS) δ = 17.78 (CH_3), 44.44 (C_5 and C_6), 112.34 (C_3), 126-137 (aryl), 160.29 (C_2), 189.55 ppm (C_4); ms: (relative intensity, %) 405 (100), 266 (60), 134 (32), 118 (35).

Anal. Calcd. for $C_{24}H_{20}ClNOS$: C, 71.01; H, 4.97; N, 3.45. Found: C, 71.07; H, 4.94; N, 3.43.

2-Anilino-5,6-dihydro-3-(4-methoxyphenyl)-6-phenyl-4*H*-thiopyran-4-one, **5e**.

Method A gave a yellow compound. The crude product was refluxed in ethanol for 6 hours, and the solution was cooled to room temperature. The precipitated compound was isolated, washed with a small portion of dry ether, and recrystallized from toluene, yield 1.2 g (30%), mp 187-189°; ir: 1620 (C=O) 2260 cm^{-1} (NH); uv: λ max (log ε) = 254 (4.15), 334 nm (4.30); ^{1}H-nmr (deuteriochloroform/TMS): δ = 3.0 (H_c), 3.2 (H_b), 3.8 (s, 3H, OCH_3), 4.7 (H_a), 6.5 (broad, 1H, NH), 7.0-7.5 ppm (m, 14H, aryl); ^{13}C-nmr (deuteriochloroform/TMS): δ = 44.76 (C_5 or C_6), 45.21 (C_5 or C_6), 55.09 (OCH_3), 112.75 (C_3), 114-159 (aryl), 159.22 (C_2), 190.49 ppm (C_4); ms: (relative intensity, %) 387 (100), 282 (100), 282 (81), 164 (41), 148 (27), 77 (33).

Anal. Calcd. for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61. Found: C, 73.97; H, 5.41; N, 3.54.

2-Anilino-3-carboethoxy-5,6-dihydro-6,6-dimethyl-4*H*-thiopyran-4-one, **9a**.

Method B was used. The isolated crystals were recrystallized from ethyl acetate/cyclohexane, yield 1.7 g (44%), mp 106-107°; ir: 1650 (C=O), 3440 cm^{-1} (NH); uv: λ max (log ε) = 247 (4.02), 306 nm (4.26); ^{1}H-nmr (deuteriochloroform/TMS): δ = 1.41 (s, 6H, 2 x CH_3), 2.70 (s, 2H, CH_2), 1.40 (t, 3H, CH_3 J = 7 Hz), 4.36 (q, 2H, CH_2 J = 7 Hz), 7.30 (s, 5H, aryl), 12.14 ppm (broad, 1H, NH); ^{13}C-nmr (deuteriochloroform/TMS): δ = 43.7 (C_6), 53.8 (C_5), 98.5 (C_3), 171.4 (C_2), 187.4 ppm (C_4); ms: (relative intensity, %) 305 (66), 259 (100), 144 (24), 143 (24), 77 (15).

Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.92; H, 6.27; N, 4.59. Found: C, 63.20; H, 6.30; N, 4.56.

2-Anilino-3-carboethoxy-5,6-dihydro-6-(spirocyclopentyl)-4*H*-thiopyran-4-one, **9b**.

Method B was used. The isolated crystals were recrystallized from cyclohexane, yield 2.0 g (32%), mp 133-134°; ir: 1640 (C=O), 3440 cm^{-1} (NH); uv: λ max (log ε) = 249 (411), 308 nm (4.33); ^{1}H-nmr (deuteriochloroform/TMS): δ = 1.40 (t, 3H, CH_3 J = 7 Hz), 1.7-1.8 (m, 8H), 2.8 (s, 2H, CH_2), 4.33 (q, 2H, CH_2 J = 7 Hz), 7.2-7.5 (s, 5H, aryl), 12.14 ppm (broad, 1H, NH); ^{13}C-nmr (deuteriochloroform/TMS): δ = 52.2 (C_5), 53.1 (C_6), 99.3 (C_3), 172 (C_2), 189.6 ppm (C_4); ms: (relative intensity, %) 331 (38), 285 (100), 252 (20), 144 (58), 77 (88).

Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.38; N, 4.25. Found: C, 65.31; H, 6.42; N, 4.17.

2-Anilino-3-carboethoxy-5,6-dihydro-6-(spirocyclohexyl)-4*H*-thiopyran-4-one, **9c**.

The crude product from method B was recrystallized from ethyl acetate/cyclohexane, yield 2.1 g (61%), mp 144-145°; ir: 1640 (C=O), 3440 cm^{-1} (NH); uv: λ max (log ε) = 248 (4.05), 307 nm (4.27); ^{1}H-nmr (deuteriochloroform/TMS): δ = 1.4 (t, 3H, CH_3 J = 7 Hz), 1.4-1.7 (m, 10H), 2.76 (s, 2H, CH_2), 4.32 (q, 2H, CH_2 J = 7 Hz), 7.3 (s, 5H, aryl), 12.13 ppm (broad, 1H, NH); ^{13}C-nmr (deuteriochloroform/TMS): δ = 48.4 (C_6), 52.3 (C_5), 98.9 (C_3), 170 (C_2), 189.1 ppm (C_4); ms: (deuteriochloroform/TMS) 345 (66), 299 (94), 232 (72), 144 (94), 77 (100).

Anal. Calcd. for $C_{19}H_{23}NO_3S$: C, 66.05; H, 6.71; N, 4.05. Found: C, 65.93; H, 6.68; N, 4.48.

Synthesis of 1,4-Diaryl-5-methylthio-3-oxo-1,4-pentanediene, **6**.

General Method.

To a stirred solution of **1** (10 mmoles) in anhydrous dimethyl sulfoxide (20 ml), an equimolar amount of sodium methoxide, dissolved in dry methanol (4 ml), was added, and the stirring continued for 20 minutes at room temperature. Phenylisothiocyanate (10 mmoles) was added, followed by another 15 minutes of stirring, before methyl iodide (30 mmoles) was added. After 45 minutes of stirring at 60°, the reaction mixture was cooled, poured into cold water (300 ml, 0°), and treated with 1 molar hydrochloric acid (to *p*H = 2). The resulting orange oil was isolated, dissolved in methylene chloride (200 ml), dried with sodium sulphate, evaporated *in vacuo*, and recrystallized from ethanol, giving orange crystals.

5-Anilino-1,4-diphenyl-5-methylthio-3-oxo-1,4-pentanediene, **6a**.

The general method gave **6a** as orange crystals, yield 0.9 g (23%), mp 122-124°; ir: 1630 cm^{-1} (C=O); uv: λ max (log ε) = 310 (4.13), 414 nm (4.38); ^{1}H-nmr (deuteriochloroform/TMS): δ = 1.8 (s, 3H, CH_3), 6.5 (d, 1H, CH J = 16 Hz), 7.1-7.5 (m, 15H, aryl), 7.6 (d, 1H, CH J = 16 Hz), 14.3 ppm (s, 1H, NH); ^{13}C-nmr (deuteriochloroform/TMS): δ = 16.98 (CH_3), 183.90 ppm (C_3); ms: (relative intensity, %) 371 (33), 324 (38), 294 (11), 131 (100), 103 (44), 89 (21).

Anal. Calcd. for $C_{24}H_{21}NOS$: C, 77.59; H, 5.70; N, 3.77. Found: C, 77.97; H, 5.75; N, 3.64.

5-Anilino-1-(4-methylphenyl)-5-methylthio-3-oxo-4-phenyl-1,4-pentanediene, **6b**.

The general method gave **6b** as orange crystal, yield 1.7 g (45%), mp 110-112°; ir: 1630 cm^{-1} (C=O), uv λ max (log ε) = 320 (4.07), 415 nm

(4.35); ^{1}H-nmr (deuteriochloroform/TMS): δ = 1.8 (s, 3H, SCH_3), 2.3 (s, 3H, aryl-CH_3), 6.5 (d, 1H, CH J = 16 Hz), 7.1-7.5 (m, 14H, aryl), 7.6 (d, 1H, CH J = 16 Hz), 14.3 ppm (s, 1H, NH); ^{13}C-nmr (deuteriochloroform/TMS): δ = 16.87 (s-CH_3), 21.19 (aryl-CH_3), 184.32 ppm (C_3); ms: 385 (60), 338 (14), 220 (100), 192 (27), 89 (57).

Anal. Calcd. for $C_{25}H_{23}NOS$: C, 77.89; H, 6.01; N, 3.63. Found: C, 78.07; H, 6.07; N, 3.49.

Acknowledgements.

Experimental details from Dr. R. Bodalski describing the preparation of starting materials **7** are gratefully acknowledged.

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[6] This is an AMX pattern and not an ABX pattern as suggested in the previous paper, see ref [1].