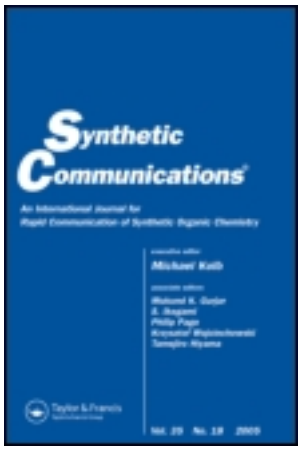

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Synthesis of Thiochromen-4-one-annelated Heterocycles: Regioselective Cyclization of 3-Hydroxy-2-cyclohex-2′-enylthiochromen-4-one

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Synthesis of Thiochromen-4-one-annelated Heterocycles: Regioselective Cyclization of 3-Hydroxy-2-cyclohex-2′-enylthiochromen-4-one

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ABSTRACT

2-Cyclohex-2′-enyl-3-hydroxythiochromen-4-one (**4**) was synthesized in 80% yield by the thermal [3,3] sigmatropic rearrangement of 3-cyclohex-2′-enyloxythiochromen-4-one (**3**). Treatment of **4** with palladium (*bis*benzonitrile) chloride in refluxing benzene afforded linearly cyclized product, tetrahydrobenzofuro[3,2-*b*]thiochromen-6-one (**5**) in 98% yield which on dehydrogenation with palladized charcoal gave benzofuro[3,2-*b*]thiochromen-6-one (**6**). Substrate **4** on reaction with hexamethylenetetramine hydrotribromide gave a mixture of three products, linearly cyclized heterocycle **10** (35%), bicyclic heterocyclic **8** (15%), and dibromide **9** (20%). The same reaction when conducted with pyridine hydrotribromide furnished only the

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dibromide **9** which was then cyclized in acetone–potassium carbonate to give the bicyclic compound **8** in 85% yield. The dibromide **9** was cyclized by heating with palladized charcoal in diphenyl ether to give a mixture of linearly cyclized product **5** (7%) and bicyclic product **8** (63%). Substrate **4** was also cyclized in cold conc. H_2SO_4 to give a bicyclic product **11** in 95% yield.

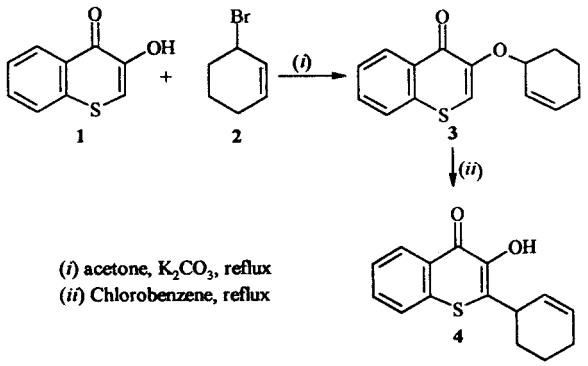
INTRODUCTION

The thieno[2,3-*b*]benzothiapyran-4-one skeleton is an intermediate in the synthesis of a series of drugs[1] used against psychotic disturbances. Recently we reported[2] a simple synthesis for this heterocyclic system. The importance of the thieno[2,3-*b*]benzothiapyran-4-one system prompted us to undertake a study on the structural modification of the lead compound by altering the ring fusion and replacing the thiophene ring by a furan ring. We have recently reported some results.[3–5] We now wish to report the results of our investigation on the synthesis of related heterocycles by the cyclization of 3-hydroxy-2-(cyclohex-2′-enyl) thiochromen-4-one (**4**).

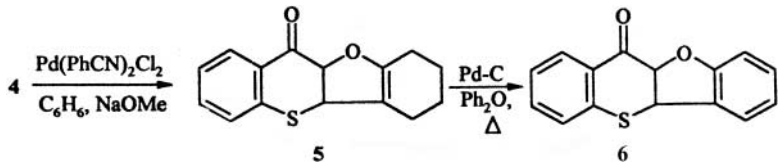
RESULTS AND DISCUSSION

Thermal [3,3] sigmatropic rearrangement of 3-cyclohex-2′-enyloxy-thiochromen-4-one (**3**) in refluxing chlorobenzene for 13 h afforded 2-cyclohex-2′-enyl-3-hydroxythiochromen-4-one (**4**), the starting material for this study. Compound **3** was in turn prepared from the reaction of 3-bromocyclohexene (**2**) with 3-hydroxythiochromen-4-one (**1**) in refluxing acetone in the presence of anhydrous potassium carbonate (Sch. 1).

Three different approaches were considered for the cyclization of substrate **4**. Recently there has been a lot of interest in the palladium catalyzed[6] synthesis of heterocyclic compounds. This aroused our interest to apply this reaction to the synthesis of heterocycle from substrate **4**. Accordingly, substrate **4** was treated with palladium chloride *bis*benzonitrile in refluxing benzene in the presence of sodium methoxide for 5 h to give a linear heterocyclic compound **5** in 98% yield. Compound **5** on treatment with palladized charcoal in diphenyl ether at 160°C for 1.5 h gave aromatized product **6** (Sch. 2).

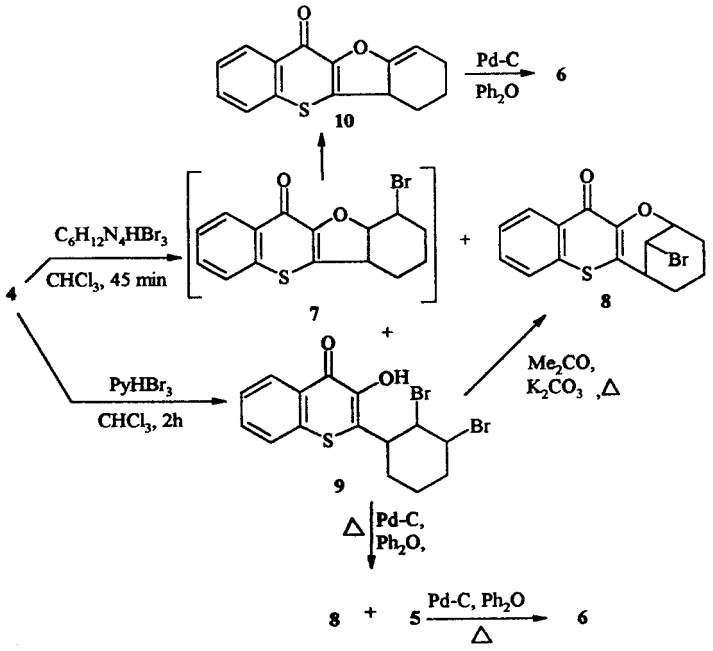


Scheme 1.



Scheme 2.

Our second approach for the cyclization of substrate **4** involved its reaction with pyridine hydrotribromide and hexamethylenetetramine hydrotribromide. Recently these two reagents have been used for the synthesis of heterocycles from *o*-alkenyl phenols and enols.[7] Substrate **4** was treated with hexamethylenetetramine hydrotribromide in chloroform at 0–5°C for 45 min to give a mixture of three different products viz, linear heterocycle **10** (35%), bicyclic heterocycle **8** (15%), and the dibromide **9** (20%). The linear heterocycle **10** was dehydrogenated with palladized charcoal in diphenyl ether at 160°C for 2 h to give aromatic compound **6** (95%) (Sch. 3). However, substrate **4** on treatment with pyridine hydrotribromide in chloroform at 0–5°C for 2 h furnished only the dibromide **9** in 90% yield. Dibromide **9** when refluxed in acetone with anhydrous potassium carbonate for 1 h gave the bicyclic heterocycle **8** in 85% yield. However, when the dibromide **9** was refluxed with palladized charcoal in diphenyl ether for 1.5 h gave a mixture of two products viz, compound **8** (63%) and compound

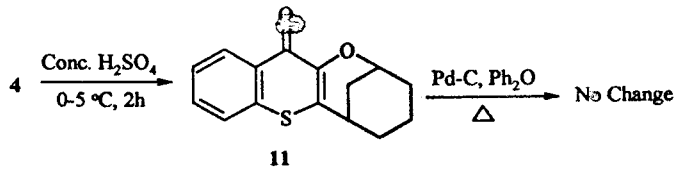


Scheme 3.

5 (7%). Compound **5** was dehydrogenated to give aromatic compound **6** (Sch. 3).

Our third approach for the cyclization of substrate **4** towards the synthesis of heterocyclic compound involved the use of conc. H_2SO_4. There are numerous examples of cyclization of *o*-alkenyl phenols and enols in recent literature for the synthesis of heterocyclic compounds.[8] Accordingly, substrate **4** was treated with cold conc. H_2SO_4 at 0–5°C to give the bicyclic heterocycle **11** in almost quantitative yield. Product **11** remained unaffected when refluxed with palladized charcoal in diphenyl ether for 2 h (Sch. 4). This indicates the bicyclic nature of this product.

Cyclization of 3-hydroxy-2-cyclohex-2′-enylthiochromen-4-one (**4**) with palladium chloride *bis*benzonitrile and conc. H_2SO_4 and is regioselective and the cyclization of the dibromide **9** with acetone–potassium carbonate is also regioselective. Only one product in each case is obtained in excellent yield. However, the cyclization of **4** with hexamethylenetetramine hydrotribromide is not regioselective. The



11

Scheme 4.

initially formed bromonium ion gives three different products viz, linear heterocycle **10** by "5-exo" process, bicyclic heterocycle **8** by a "6-endo" cyclization, and the dibromide **9** by SN_2 displacement by Br^-.

EXPERIMENTAL

Melting points were determined in a sulfuric acid bath and are uncorrected. UV absorption spectra were recorded on a Shimadzu UV-160A spectrophotometer (absolute ethanol). IR spectra were run on a Perkin-Elmer 1330 apparatus. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker 300 MHz spectrometer. Elemental analyses data (data in accord with the calculated values) and mass spectra were recorded by RSIC (CDRI), Lucknow. Silica (60–120 mesh) was obtained from Spectrochem (India). Extracts were dried over anhydrous Na_2SO_4.

Preparation of 3-(2′-Cyclohexenyloxy)-thiochromen-4-one (3)

A mixture of 3-hydroxythiochromen-4-one (**1**) (0.5 g, 2.25 mmol) and 3-bromocyclohexene (**2**) (2.25 mmol) in dry acetone (50 mL) was refluxed in presence of K_2CO_3 (2 g) for 6 h. The solvent was evaporated and the residual mass was extracted with $CHCl_3$ (3×25 mL) and dried (Na_2SO_4). Chloroform was distilled off and the residue was then purified by column chromatography over silica gel (60% starting material remained unchanged). The product **3** was eluted with benzene.

Compound 3: Yield 70%; viscous liquid; λ_{max}/nm 225, 266, 358; ν_{max}/cm^{-1} 3040, 2930, 1620, 1590, 1400; δ_H (300 MHz): 1.67–2.17 (m, 6H), 4.84 (s, 1H), 5.89–6.00 (m, 2H), 7.19 (s, 1H), 7.47–7.67 (m, 3H),

8.59 (d, $J = 7.86$ Hz, 1H); m/z 258 (M^+); (Found: C, 69.63; H, 5.49; S, 12.35. $C_{15}H_{14}O_2S$ requires C, 69.77; H, 5.43; S, 12.40%).

Thermal Rearrangement of Compound 3 to Compound 4

Compound 3: (0.51 g, 2 mmol) in chlorobenzene (3 mL) was refluxed for 12–14 h. The reaction mixture was then column chromatographed over silica gel. The product **4** was eluted with benzene:petroleum ether (1:1) and recrystallized from petroleum ether.

Compound 4: Yield 80%; m.p.: 146°C; λ_{max}/nm 241, 351; ν_{max}/cm^{-1} 3295, 3020, 2920, 1580, 1440; δ_H (300 MHz): 1.71–1.85 (m, 3H), 2.12–2.14 (m, 3H), 4.18–4.22 (m, 1H), 5.72–5.76 (m, 1H), 6.04–6.08 (m, 1H), 7.49–7.64 (m, 3H), 7.67 (brs, 1H, D_2O exchangeable), 8.53 (d, $J =$ 7.73 Hz, 1H); m/z 258 (M^+); (Found: C, 69.86; H, 5.60; S, 12.52. $C_{15}H_{14}O_2S$ requires C, 69.77; H, 5.43; S, 12.40%).

Palladium (*Bis*benzonitrile) Chloride Cyclization of Compound 4 to Compound 5

To compound **4** (250 mg, 1 mmol) in thiophene free dry benzene (20 mL), sodium methoxide (55 mg, 1 mmol) and palladium (*bis*benzonitrile) chloride (425 mg, 1 mmol) were added and refluxed on water bath for 5 h. Then the reaction mixture was filtered and benzene was distilled off from the filtrate. The residual mass was purified by column chromatography over silica gel. The product **5** was eluted with ethyl acetate:benzene (1:9) and recrystallized from chloroform–petroleum ether.

Compound 5: Yield 98%; m.p.: 190°C; λ_{max}/nm 270, 309, 348; ν_{max}/cm^{-1} 3060, 2930, 1620, 1560, 1500, 1450; δ_H (300 MHz): 1.86–1.99 (m, 4H), 2.56 (m, 2H), 2.83 (m, 2H), 7.52–7.71 (m, 3H), 8.74 (d, $J = 8.22$ Hz, 1H); m/z 256 (M^+); (Found: C, 70.54; H, 5.46; S, 12.59. $C_{15}H_{14}O_2S$ requires C, 70.34; H, 4.69; S, 12.50%).

Aromatization of Compound 5 to Compound 6

The compound **5** (125 mg, 0.5 mmol) in diphenyl ether was heated at 160°C with palladized charcoal for 1.5 h and then the reaction mixture was column chromatographed over silica gel. The compound **6** was eluted with ethyl acetate:benzene (1:9) and recrystallized from petroleum ether.

Compound 6: Yield 98%; m.p.: 204–206°C; λ_{max}/nm 216, 270, 312, 363; ν_{max}/cm^{-1} 3060, 1620, 1520, 1440; δ_H (300 MHz): 7.42–7.47 (m, 1H), 7.61–7.85 (m, 6H), 8.79 (m, 1H); *m/z* 252 (M^+); (Found: C, 71.62; H, 3.25; S, 12.52. $C_{15}H_8O_2S$ requires C, 71.43, H, 3.17, S, 12.70%).

Preparation of Compound 9 from Compound 4

The compound 4 (250 mg, 1 mmol) in chloroform (20 mL) was cooled at 0–5°C and pyridine hydrotribromide (320 mg, 1 mmol) was added slowly. The reaction mixture was stirred for 2 h and washed with water and dried (Na_2SO_4). Chloroform was distilled off and the residual mass was purified by column chromatography. The product **9** was eluted with benzene–petroleum ether (1:1) and recrystallized from petroleum ether.

Compound 9: Yield 90%; m.p.: 178°C; λ_{max}/nm 218, 266, 371; ν_{max}/cm^{-1} 3300, 3040, 2920, 1575, 1440; δ_H (300 MHz): 1.87–2.26 (m, 5H), 2.50–2.59 (m, 1H), 4.37 (d, $J = 12$ Hz, 1H), 4.82 (s, 1H), 5.21 (s, 1H), 7.51–7.69 (m, 3H), 7.82 (brs, 1H, D_2O exchangeable), 8.54 (d, $J = 7.26$ Hz, 1H); *m/z* 420, 418, 416 (M^+); (Found: C, 43.34; H, 3.49; S, 7.42. $C_{15}H_{14}O_2SBr_2$ requires C, 43.06; H, 3.34; S, 7.65%).

Cyclization of Compound 9 to Compound 8

The compound **9** (100 mg, 0.25 mmol) in dry acetone (10 mL) was refluxed with potassium carbonate (0.2 g) for 1 h. Acetone was distilled off and the residue was extracted with chloroform (3×15 mL). The extract was washed with water and dried (Na_2SO_4). Chloroform was distilled off and the residual mass was purified by column chromatography. The product **8** was eluted with ethyl acetate:benzene (1:9) and recrystallized from chloroform–petroleum ether.

Compound 8: Yield 85%; m.p.: 260°C; λ_{max}/nm 218, 263, 366; ν_{max}/cm^{-1} 3030, 2900, 1580, 1440; δ_H (300 MHz): 1.60–1.62 (m, 2H), 1.78–1.80 (m, 1H), 1.99–2.10 (m, 1H), 2.15–2.17 (m, 1H), 2.38–2.43 (m, 1H), 3.15 (m, 1H), 4.44–4.60 (m, 1H), 4.85–4.86 (m, 1H), 7.47–7.58 (m, 3H), 8.63 (m, 1H); *m/z* 338, 336 (M^+); (Found: C, 53.55; H, 4.03; S, 9.34. $C_{15}H_{13}O_2SBr$ requires C, 53.31; H, 3.86; S, 9.49%).

Cyclization of Compound 9 with Palladized Charcoal

The compound **9** (100 mg, 0.25 mmol) in diphenyl ether (2 mL) was refluxed with 10% palladized charcoal (200 mg) for 2 h. The reaction mixture was chromatographed over silica gel. Yield of the reaction was 70 mg (70%) of which 7% was compound **5** and 63% was compound **8**.

Reaction of Compound 4 with Hexamethylenetetramine Hydrotribromide

The compound **4** (520 mg, 2 mmol) in chloroform (20 mL) was cooled at 0–5°C and hexamethylenetetramine hydrotribromide (770 mg, 2 mmol) was added slowly. The reaction mixture was stirred for 45 min and washed with water and dried (Na_2SO_4). Chloroform was distilled off and residual mass was purified by column chromatography over silica gel. The product **9** was eluted with benzene–petroleum ether (1:1) and the product **8** and **10** were eluted with ethyl acetate–benzene (1:9).

Compound 10: Yield 35%; m.p.: 185°C: λ_{max}/nm 223, 272, 307, 353; ν_{max}/cm^{-1} 3040, 2920, 1600, 1580, 1440; δ_H (300 MHz): 1.90–2.75 (m, 7H), 5.39 (t, $J = 3.39$, 1H), 7.53–7.71 (m, 3H), 8.73 (m, 1H); m/z 256 (M^+); (Found: C, 70.26; H, 4.78; S, 12.57. $C_{15}H_{12}O_2S$ requires C, 70.34; H, 4.69; S, 12.50%).

Cyclization of Compound 4 to Compound 11 with Sulphuric Acid

The compound **4** (250 mg, 1 mmol) was slowly added to a cold conc. H_2SO_4 (3 mL) at 0–5°C and stirred for 2 h. The reaction mixture was poured into crushed ice and extracted with chloroform (3×25 mL). The chloroform was washed with Na_2CO_3 solution (2×25 mL), water (2×25 mL) and dried (Na_2SO_4). Chloroform was distilled off and the residual mass was purified with column chromatograph over silica gel. The product **11** was eluted with ethyl acetate–benzene (1:9) and recrystallized from benzene.

Compound 11: Yield 95%; m.p.: 150°C; λ_{max}/nm 218, 264, 367; ν_{max}/cm^{-1} 3030, 2910, 1580, 1440; δ_H (300 MHz): 1.81–2.28 (m, 8H), 2.87 (s, 1H), 4.86 (s, 1H), 7.43–7.55 (m, 3H), 8.60 (d, $J = 8.19$, 1H); m/z

258 (M^+); (Found: C, 69.66; H, 5.63; S, 12.62. $C_{15}H_{14}O_2S$ requires C, 69.77; H, 5.43; S, 12.40%).

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