Synthesis of 4*H*-Thiopyran-4-ones

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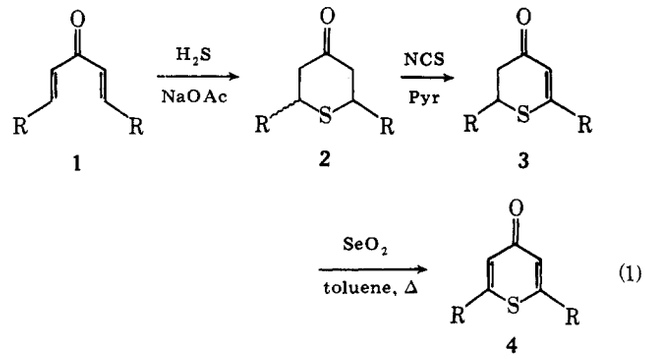
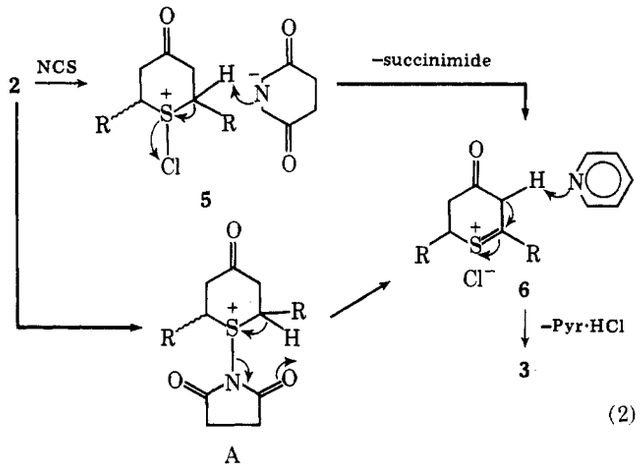
4*H*-Thiopyran-4-ones (4) are of considerable theoretical interest and practical use.[1] Although their chemistry has been studied since the turn of this century, methodology toward their synthesis has been little explored. As part of our investigation of the synthesis of pyrylium dyes,[2] we required large amounts of 2,6-diphenyl-4*H*-thiopyran-4-one and its derivatives 4 as intermediates. The published procedures were unsatisfactory since the yields were low and difficult to reproduce. For example, 2,6-diphenyl-4*H*-thiopyran-4-one (4, R = Ph) was prepared in poor yield (15%) by reaction of the corresponding tetrahydro derivative 2 (R = Ph) with PCl_5 followed by treatment with base.[3] The same procedure, when applied to the 2,6-dianisyl derivative (2, R = anisyl), was reported to give only 3,5-dichloro-2,6-dianisyl-4*H*-thiopyran-4-one instead of the desired 4 (R = anisyl).[4] Similarly, the best yield published for the parent 4*H*-thiopyran-4-one (4, R = H) was only 37% by a slightly modified procedure.[5] Other methods such as the direct cyclization of diacetylenic ketones with thioureas and mercaptans occur readily but often unpredictably giving a mixture of products containing mostly the isomeric thiacyclopentenone derivative instead of 4.[6] We wish to report a useful and apparently general synthesis of 4*H*-thiopyran-4-one (eq 1).



1 2 3 4 (1)

The ketone 1 was converted to the tetrahydro-4*H*-thiopyran-4-one (2) as reported by Arndt,[3] and then converted to 4 via the dihydro-4*H*-thiopyran-4-one (3). The latter was prepared by a mild oxidative elimination reaction employing *N*-chlorosuccinimide (NCS) and pyridine as reagents.[7] Presumably, 2 is initially oxidized by NCS to generate a chlorosulfonium salt 5,[8] followed by formation of 6 with concurrent loss of succinimide (eq 2). Under the basic conditions (pyridine) in which these reactions were conducted, the most acidic hydrogen, which clearly is the hydrogen α to both the carbonyl and sulfur stabilized carbonium ion in 6, is readily eliminated yielding the desired dihydro-4*H*-thiopyran-4-ones (3). Alternatively, it has recently been suggested that the NCS oxidation of sulfides may involve the intermediacy of a succinimidosulfonium salt of type A, and 6 can be generated intramolecularly by syn elimination of succinimide.[9]

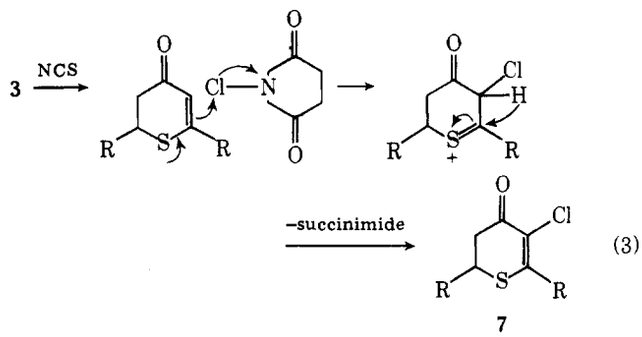
Several derivatives of 2 were converted to their corresponding 4*H*-thiopyran-4-ones (Table I) to reflect the general



5 6 3 A (2)

synthetic application of this new approach. Yields of 2 were excellent. Because of the diastereoisomeric nature of 2 obtained from the hydrogen sulfide cyclization, these compounds were not rigorously purified, and in most cases were found suitable for use in the subsequent reactions. Selenium dioxide dehydrogenation was done in a conventional manner.[10] We prefer to use toluene rather than traditional high-boiling alcohols (e.g., butanol) as solvent for ease of workup, though the latter were found equally satisfactory. Numerous other dehydrogenation reagents were also tried including DDQ, chloranil, Pd/C, and sulfur under a variety of reaction conditions, none of which were entirely satisfactory, and the results were much inferior to that of the selenium dioxide dehydrogenation.

It is of interest to note that direct dehydrogenation (e.g., SeO_2) of the tetrahydro derivative 2 to give 4*H*-thiopyran-4-ones 4 was unfruitful.[1] The introduction of the first double bond into the heterocyclic system by our approach apparently provides the necessary driving force for the subsequent dehydrogenation (3 → 4). Furthermore, the reaction of 3 (R = Ph) with 1 mol of NCS resulted in the exclusive formation of 3-chloro-2,6-diphenyl-5,6-dihydro-4*H*-thiopyran-4-one (7, R = Ph),[11] which presumably resulted from an electrophilic substitution on the vinyl sulfide moiety of 3[12] (eq 3).



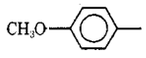
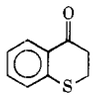
7 (3)

Experimental Section[13]

The following experiments are illustrative of the general synthetic procedures.

2,6-Diphenyldihydro-4*H*-thiopyran-4-one (3, R = Ph). To an ice-cooled, well-stirred solution of 50.4 g (0.189 mol) of 2,6-diphenyl-4*H*-tetrahydrothiopyran-4-one[3] (mp 87–90 °C) and 15 g (0.19 mol) of pyridine in 400 mL of methylene chloride, 26 g (0.19 mol) of NCS in powdered form was added over a 15-min period. The reaction mixture was allowed to equilibrate slowly to ambient temperature

Table I. Synthesis of 4*H*-Thiopyran-4-ones[13]

R	2[e] Mp (bp), °C	2[e] Yield,[a] %	3[f] Mp (bp), °C	3[f] Yield, %	4[g] Mp (bp), °C	4[g] Yield,[a] %
Ph	87–89[2]	100[3]	(115–130, 2.4 μ) 51–54	100[a] (93)[b]	120–125 (131–132)[c]	98
	85–89	95	89	47[b]	149.7	89
	168–169	77[4]	115.4	100[a]	158.6	88
H	59–61		(56–58, 0.9 mm)[15]	100[a] (92)[b]	105–107[16]	62[d]
	(154, 12 mm)		70–71[17]	100[a] (96)[b]		

[a] Yield of substantially pure product which is suitable for subsequent use. [b] Yield of analytically pure product. [c] Analytical sample obtained by recrystallization from EtOAc (lit.[3] mp 132–133 °C). [d] Some Se-containing by-products were also formed, but not characterized (cf. ref 10). [e] Registry no. are, respectively, 37014-01-0, 62461-51-2, 2573-84-4, 1072-72-6, 3528-17-4. [f] Registry no. are, respectively, 60839-95-4, 62461-52-3, 62461-53-4, 57242-69-0, 491-39-4. [g] Registry no. are, respectively, 1029-96-5, 62461-54-5, 62461-55-6, 1003-41-4.

over a 2-h period followed by a period of 2 h at room temperature. Methylene chloride was removed under vacuum at 30–35 °C and replaced with 400 mL of ether. The insoluble, precipitated succinimide was broken up manually, removed by filtration, and washed thoroughly with ether until colorless. The combined ethereal extract was dried ($MgSO_4$) and concentrated to give 51 g (~100%) of essentially pure (assay by TLC) product as a light brown, viscous oil. NMR [δ 3.05 [t, 2, $-C(=O)CH_2CH(S)Ph$], 4.65 [dd, 1, $-CH_2CH(S)Ph$], 6.5 (s, 1, $-CH=CPh$), and 7.4 (m, 10, ArH)] showed the crude material to contain only traces of ether as a contaminant. An analytical sample was obtained by vacuum distillation of a portion (8 g) of this material at bp 115–130 °C (2–4 μ), from which 7.0 g (93%) of pure 2,6-diphenyl-4*H*-dihydrothiopyran-4-one was isolated (slowly crystallized on standing, mp 51–54 °C).

2,6-Bis(2-thienyl)tetrahydro-4*H*-thiopyran-4-one (2, R = 2-Thienyl). A mixture of 24 g (0.097 mol) of bis(2-thienal)acetone (prepared in quantitative yield by the procedure described for the preparation of dibenzalacetone),[14] 20 g of sodium acetate, and 200 mL of alcohol was refluxed while hydrogen sulfide was passed slowly into the solution for 5 h. The mixture was chilled, and the solid was collected and washed with water. The filtrate was diluted with 100 mL of water and extracted with methylene chloride. The extract was dried ($MgSO_4$) and the solvent removed. The solid residue was combined with the original solid to give 25 g (91%) of product: mp 85–89 °C; NMR δ 3.0 (m, 4, methylenes), 4.54 (m, 2, methines) and 6.7–7.2 (m, 6, thiophene).

2,6-Bis(2-thienyl)dihydro-4*H*-thiopyran-4-one (3, R = 2-Thienyl). To an ice-cooled and well-stirred solution of 15 g (0.0535 mol) of **2** (R = 2-thienyl) and 4.65 g (0.059 mol) of pyridine in 200 mL of methylene chloride was added 7.4 g (0.054 mol) of powdered NCS in ca. 10 min. The brown solution was allowed to slowly equilibrate to ambient temperature under nitrogen for 4 h and worked up by washing with 200 mL of water. Methylene chloride extracts were separated and concentrated in vacuo to give 14.7 g of a dark brown, gummy solid which was purified by column chromatography (silica gel, Wöelm dry column grade activity III, 1.75 × 19 in. column, wet packed with hexanes). Elution with benzene–hexanes (1:1 v/v) afforded first 2.4 g of unreacted starting material followed by a total of 5.95 g (47% based on consumed **2**) of the desired crystalline product: NMR δ 2.95 (d, J = 8 Hz, 2, methylene), 4.74 (t, J = 8 Hz, 1, methine), 6.27 (s, 1, olefinic), and 6.45–7.5 (m, 6, thiophene); mass spectrum m/e 278 (M^+). An analytical sample was obtained by recrystallization, mp 89 °C (hexanes).

2,6-Bis(2-thienyl)-4*H*-thiopyran-4-one (4, R = 2-thienyl). A mixture of 3.4 g (0.0122 mol) of **3** (R = 2-thienyl) and 1.9 g (0.017 mol) of selenium dioxide in 100 mL of toluene was subjected to azeotropic distillation for 25 h (or until TLC assay showed the disappearance of starting material). The toluene solution, after being freed from deposited selenium metal, was concentrated in vacuo giving 3.05 g (89%) of an essentially pure crop of brown, crystalline product: NMR δ 6.8 (m, 4) and 7.1 (m, 4); mass spectrum m/e 276 (M^+), 248 ($M^+ - CO$). An analytical sample was obtained by recrystallization from benzene and hexanes in the form of dark purple needles, mp 149.7 °C.

Registry No.—**1** (R = 2-thienyl), 62461-56-7; **1** (R = Ph), 538-58-9; **1** (R = MeO-*p*-C_6H_4), 2051-07-2; **1** (R = H), 1890-28-4; acrylophenone, 768-03-6.

References and Notes

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(13) Melting points are uncorrected; NMR spectra were recorded in $CDCl_3$ on Varian T-60 and A-60 spectrometers using Me_4Si as internal standard. Mass spectra were obtained on an AEI MS-30 mass spectrometer. Elemental analyses were done by the Analytical Sciences Division, Kodak Research Laboratories, Rochester, N.Y. Satisfactory analytical data (±0.4% for C, H, S) were reported for all compounds listed in the table.
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Reductive Coupling of 1,3-Dithiolium with Zinc

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This note describes the synthesis of 2,2′-bi(dithiolyl) (1), in excellent yield, by a zinc reductive coupling reaction. A