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[5C + 1S] Annulation: A Facile and Efficient Synthetic Route toward Functionalized 2,3-Dihydrothiopyran-4-ones

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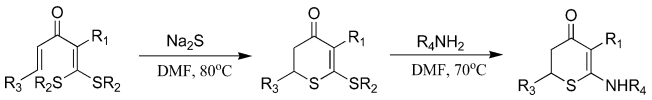

A facile and efficient synthetic route toward highly substituted 2,3-dihydrothiopyran-4-ones **2** has been developed via a formal [5C + 1S] annulation of readily available α-alkenoyl ketene-(*S,S*)-acetals **1** with sodium sulfide nonahydrated salt ($Na_2S·9H_2O$) and utilized in the synthesis of 2-(4-chlorophenyl)-6-(morpholin-4-yl)-4*H*-thiopyran-4-one **5l**, an inhibitor of DNA-dependent protein kinase (DNA-PK).

In the past decades, thiopyrone derivatives including types of thiin-4-ones, 4-thianones, and 2,3-dihydrothiopyran-4-ones have gained increasing attention for both the interest of such heterocycles themselves and their importance as key units in medicinal chemistry and versatile intermediates in organic synthesis.[1] Particularly, 2,3-dihydrothiopyran-4-ones have been used in the construction of analogues of natural products, such as tetrahydrodicranenone B,[2] pheromones,[3] thromboxanes,[4] and cyclopentanoids.[5] Recently, Ward and co-workers have utilized 4-*O*-silyloxy-2*H*-thiopyrans derived from the 2,3-dihydrothiopyran-4-ones as effective surrogates for unreactive *cis*-dienes in Diels−Alder cycloaddition processes.[6] So far, a variety of synthetic procedures are already available for the preparation of 2,3-dihydrothiopyran-4-ones, including (i) cycloaddition of structurally appropriate acetylenic/divinyl ketones with hydrogen sulfide,[3,7] (ii) intramolecular Michael addition of thiolate to an α,β-unsaturated carbonyl group,[8] (iii) Diels−Alder cycloadditions involving thiophosgene and donor-substituted thioaldehydes, respectively,[9] (iv) conjugate additions to thiin-4-ones or oxidation of 4-thianones with *N*-chlorosuccinimide (NCS),[2b,4d,5e,f,6e] and (v) dimsyl anion mediated tandem fragmentation cyclization reactions of α-alkenoyl cyclic ketene-(*S,S*)-acetals.[10] However, some of these methodologies suffer from low yields, lack of generality to wide range of substrates, or formation of regioisomers. To match the increasingly scientific and practical demands for functionalized 2,3-dihydrothiopyran-4-ones, it is still of continued interest and great importance to explore novel and efficient synthetic approaches for such thia-heterocycles.

During the course of our studies on the chemistry of α-oxo ketene-(*S,S*)-acetals,[11] we have noted that α-alkenoyl ketene-(*S,S*)-acetals **1** show promising structural feature as novel organic intermediates for (1) double Michael acceptors serving as five-carbon 1,5-bielectrophilic species, (2) dense and flexible substitution patterns, and (3) good leaving alkylthio groups subjecting to a nucleophilic vinyl substitution (S_NV) reaction. Most recently we developed a new synthetic strategy for the construction of highly substituted six-membered carbocycles and aza-heterocycles, relying upon the utilization of **1** as a five-carbon 1,5-bielectrophilic species in formal [5C + 1C(N)] annulations with various carbon and nitrogen nucleophilies, respectively.[12] These results and our continued interest in the development of new general methods for biologically important heterocycles[13] promoted us to expand the formal [5 + 1] synthetic strategy

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SCHEME 1

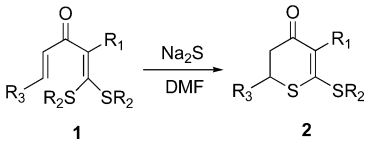


TABLE 1. Reactions of α-Alkenoyl Ketene-(*S,S*)-acetals 1 with $Na_2S·9H_2O$

entry	1[a]	R_1	R_2	R_3	time (min)	2[b]	yield[c] (%)
1	**1a**	PhCO	Et	4-MePh	25	**2a**	78
2	**1b**	PhCO	Et	3,4-OCH_2OPh	30	**2b**	75
3	**1c**	PhCO	Et	4-ClPh	20	**2c**	84
4	**1d**	PhCO	Et	2-ClPh	20	**2d**	81
5	**1e**	PhCO	Et	3-Pyridyl	15	**2e**	88
6	**1f**	PhCO	Et	PhCH=CH	30	**2f**	72
7	**1g**	PhCO	Me	4-ClPh	20	**2g**	87
8	**1h**	4-EtOPhCO	Et	4-ClPh	20	**2h**	83
9	**1i**	4-ClPhCO	Et	4-ClPh	20	**2i**	85
10	**1j**	H	Et	4-MePh	25	**2j**	80
11	**1k**	H	Et	3,4-OCH_2OPh	40	**2k**	67
12	**1l**	H	Et	4-ClPh	25	**2l**	82

[a] Substrate. [b] Product. [c] Isolated yields for compounds **2**.

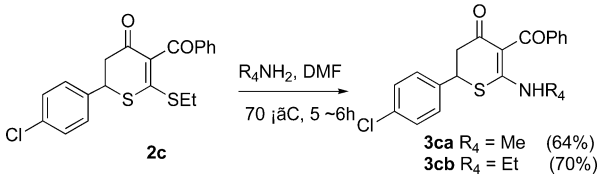
to other useful heterocyclic systems. In the present paper, we wish to report the [5C + 1S] annulation of **1** with sulfur nucleophile, $Na_2S·9H_2O$, for the synthesis of functionalized and substituted 2,3-dihydrothiopyran-4-ones.

The substrates **1** (Scheme 1 and Table 1) were readily prepared by the Aldol condensation of α-acyl ketene-(*S,S*)-acetals with varied aldehydes in the presence of ethanolic sodium hydroxide in excellent yields according to a reported procedure.[14] The reaction of **1a** with $Na_2S·9H_2O$ (3 equiv) was initially performed in DMF for 2 days. The reaction furnished a white solid after workup and column chromatography of the resulting mixture. The product was characterized as 6-ethylthio-2,3-dihydrothiopyran-4-one **2a** on the basis of its spectra and analytical data (Scheme 1). The reaction was then carried out under various conditions to optimize the reaction yield. It was found a higher temperature could dramatically reduce the reaction time to around 30 min. However, a large excess of $Na_2S·9H_2O$, 5 equiv for example, would result in a low yield of **2a**, which might be attributed to the introduction of too much hydrated water into the reaction system. The experiments revealed that 1.1 equiv of $Na_2S·9H_2O$ was sufficient for the complete conversation of **1a** to **2a** (Table 1, entry 1).

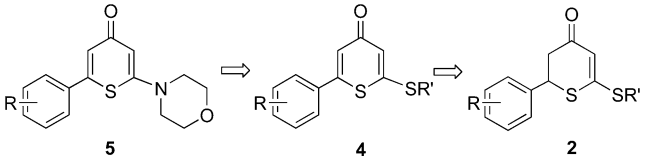
Subsequently, a range of reactions of α-alkenoyl ketene-(*S,S*)-acetals **1b**−**l** with $Na_2S·9H_2O$ were carried out under the optimal conditions, namely, 1.1 equiv of $Na_2S·9H_2O$ employed in DMF at 80 °C. Some of the results are summarized in Table 1. All of the reactions could proceed smoothly under the mild conditions within a very short reaction time to afford the corresponding 2,3-dihydrothiopyran-4-ones **2b**−**l** in good to high yields (up to 88%). It is worth noting that a variety of substituents including alkenyl (entry 6), aryl (entries 1−4, 7−12), heteroaryl (entry 5), alkylthio (entries 7 and 8), and benzoyl (entries 1−9) groups can be introduced to the dihydrothiopyran-4-one core through the modification or rational design of the stuructures of substrates **1**, i.e., the systemic variation of R_1, R_2, and R_3. Moreover, it is of interest that the substrates **1j**−**l** with a monoactivated carbonyl group (entries 10−12) can also smoothly react with sodium sulfide to yield the corresponding dihydrothiopyran-4-ones **2j**−**l** in good yields as for those substrates with doubly activated carbonyl groups such as **1a**−**i**. The results shown above demonstrate the wide scope and synthetic utility of the [5C + 1S] annulation reaction with respect to the α-alkenoyl ketene-(*S,S*)-acetals **1** with various R_1, R_2, and R_3 groups. We therefore present here a facile and efficient protocol for the synthesis of functionalized 2,3-dihydrothiopyran-4-ones **2**.

With a variety of multifunctional and substituted dihydrothiopyran-4-ones **2** in hand, we further explored the possible transformations of these functionalities to afford the novel thiopyran-4-ones. As is widely known, an alkylthio group situated at the β-carbon atom of an activated alkene can be displaced by nucleophiles via a nucleophilic vinyl substitution (S_NV) reaction.[15] Therefore, the structural feature of **2** suggests that the compounds of type **2** could be further modified with other substitution patterns at their 6-position, which may be very useful in library synthesis for the screening of potential bio- and/or pharmacological compounds. Thus, several reactions of **2** with amines were carried out. In one case, when **2c** was treated with methylamine (aqueous, 2.5 equiv) in DMF at 70 °C for 6 h, workup and column chromatography of the resulting mixture furnished a white solid (64% yield). The product was characterized as 6-methylaminothiopyrone **3ca** on the basis of its spectra and analytical data (Scheme 2). When **2c** and ethylamine were subjected to the identical conditions, 6-ethylaminothiopyrone **3cb** was obtained in 70% isolated yield.

SCHEME 2



SCHEME 3



Very recently, Hollick and co-workers synthesized and evaluated a series of 6-aryl-2-(morpholin-4-yl)-4*H*-thiopyran-4-ones **5** as potential inhibitors of the DNA repair enzyme DNA-dependent protein kinase (DNA-PK).[16] Some compounds exhibited activity superior to that of

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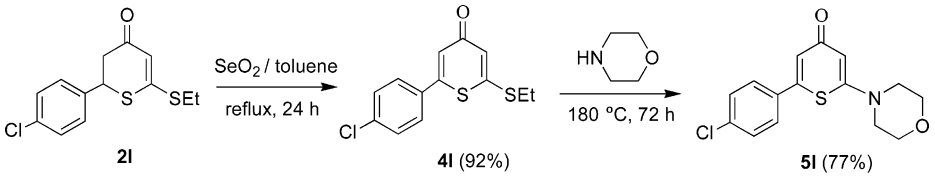
SCHEME 4



the chromenone LY294002 and were of comparable potency to the benzochromenone NU7026 (IC_{50} = 0.23 μM). In the present work, we attempt to synthesize compounds **5** using compounds **2** as precursors; the synthetic plan is depicted in Scheme 3.

Thus the dehydrogenation of **2l** with selenium dioxide was performed in refluxing toluene.[17] The reaction proceeded very cleanly to afford the desired 2-(4-chlorophenyl)-6-ethylthio-4*H*-thiopyran-4-one **4l** in 92% yield (Scheme 4). Subsequently, **4l** and morpholine (3.0 equiv) were subjected to the similar conditions employed in Scheme 2; however, the attempt did not match success, which might stem from the low reactivity based on the rigid structure of the cyclic secondary amine. Considering that the reaction might need slightly harsher conditions, we treated **4l** with morpholine in 1,3-propanediol at 180 °C. To our delight, **5l** was successfully obtained in 77% isolated yield (Scheme 4). Therefore, we provide an alternative procedure for the synthesis of 6-aryl-2-(morpholin-4-yl)-4*H*-thiopyran-4-ones.

In summary, a facile and efficient synthetic route to highly substituted 2,3-dihydrothiopyran-4-ones **2** has been developed via a formal [5C + 1S] annulation of readily available α-alkenoyl ketene-(*S,S*)-acetals **1** with $Na_2S{\cdot}9H_2O$. The versatility of the functionality, i.e., alkene, carbonyl, and alkylthio groups, makes these compounds good candidates to serve as precursors for further synthetic transformations. Indeed, the conversions of compounds **2** into 2-aryl-5-benzoyl-6-alkylamino-2,3-dihydrothiopyran-4-ones **3**, 2-alkylthio-6-aryl-4*H*-thiopyran-4-ones **4**, and 2-aryl-6-(morpholin-4-yl)-4*H*-thiopyran-4-ones **5** have been achieved. The simplicity of execution, ready availability of substrates, and broad range of potential products make this [5C + 1S] synthetic strategy most attractive for academic research and practical applications. The extension of scope and potential applications of the protocol are currently under investigation in our laboratory.

Experimental Section

General. All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 500 and 125 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400−4000 cm^{-1}. Mass spectra were recorded on LCMsD or HRMS (ESI) mass spectrometer.

Typical Procedure for Synthesis of Substituted 2,3-Dihydrothiopyran-4-ones 2 (2a as example). To a solution of α-alkenoyl ketene-(*S,S*)-acetal **1a** (0.80 g, 2 mmol) in DMF (5 mL) was added $Na_2S{\cdot}9H_2O$ (0.53 g, 2.2 mmol) in one portion at room temperature. The reaction mixture was then heated to 80 °C under stirring for about 25 min. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous Na_2CO_3 (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellowish oil. Purification was carried out by flash silica gel chromatography using petroleum/Et_2O (6:4, v/v) as eluent to give product **2a** (0.57 g, 78%).

5-Benzoyl-6-ethylthio-2-(*p*-tolyl)-2,3-dihydrothiopyran-4-one (2a). Yellowish semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.5 Hz, 3H), 2.33 (s, 3H), 2.93−3.05 (m, 3H), 3.27 (dd, J = 14.0, 16.5 Hz, 1H), 4.80 (dd, J = 3.0, 14.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.44−7.47 (m, 2H), 7.56−7.58 (m, 1H), 7.88 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 194.32, 189.82, 161.79, 138.74, 136.52, 133.36, 133.28, 131.01, 129.63, 128.95, 128.42, 127.33, 46.60, 44.09, 27.29, 20.97, 14.43. IR (KBr, cm^{-1}) 1670, 1637, 1489, 1444, 1296, 1251, 1035, 926, 813. ES-MS (*m/z*) 369.0 $[M + 1]^+$.

Typical Procedure for Synthesis of 2-Alkylamino Substituted 2,3-Dihydrothiopyran-4-ones 3 (3ca as example). To a solution of dihydrothiopyran-4-one **2c** (0.78 g, 2 mmol) in DMF (5 mL) was added 30% aqueous methylamine (0.32 mL, 5 mmol) in one portion at room temperature. The reaction mixture was then heated to 70 °C under stirring for about 6 h. After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellowish solid. Purification was carried out by flash silica gel chromatography using acetone/Et_2O (2:1, v/v) as eluent to give product **3ca** (0.46 g, 64%).

5-Benzoyl-2-(4-chlorophenyl)-6-methylamino-2,3-dihydrothiopyran-4-one (3ca). Mp 194−196 °C. ^{1}H NMR (500 MHz, DMSO) δ = 2.74 (dd, J = 2.5, 17.5 Hz, 1H), 3.02 (s, 3H), 3.08 (dd, J = 13.0, 17.5 Hz, 1H), 5.16 (dd, J = 2.5, 13.0 Hz, 1H), 7.29−7.32 (m, 2H), 7.35−7.40 (m, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 10.76 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.68, 191.03, 172.57, 143.18, 137.41, 134.08, 131.18, 130.88, 129.87, 128.91, 128.52, 107.45, 45.54, 43.46, 32.18. IR (KBr, cm^{-1}) 3419, 3056, 1634, 1590, 1557, 1370, 1281, 1090, 1013, 810, 695. ES-MS (*m/z*) 358.2 $[(M + 1)]^+$.

Preparation of 4l. To a solution of dihydrothiopyran-4-one **2l** (0.85 g, 3 mmol) in toluene (7 mL) was added SeO_2 (0.67 g, 6 mmol) in one portion at room temperature. The reaction mixture was then stirred under reflux for about 24 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellowish solid. Purification was carried out by flash silica gel chromatography using petroleum/Et_2O (2:1, v/v) as eluent to give product **4l** (0.78 g, 92%).

2-(4-Chlorophenyl)-6-ethylthio-*4H*-thiopyran-4-one (4l). Mp 70−73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.40 (t, J = 7.5 Hz, 3H), 3.09 (q, J = 7.5 Hz, 2H), 6.94 (s, 1H), 7.01 (s, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H). ES-MS (*m/z*) 282.8 $[M + 1]^+$.

Preparation of 5l. To a solution of compound **4l** (0.56 g, 2 mmol) in 1,3-propanediol (4 mL) was added morpholine (0.53 mL, 6 mmol) in one portion at room temperature. The reaction mixture was then heated to 180 °C under stirring for about 72 h. After completion of the reaction as indicated by TLC, the

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reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellowish solid. Purification was carried out by flash silica gel chromatography using petroleum/Et_2O (1:3, v/v) as eluent to give product **5l** (0.47 g, 77%).

2-(4-Chlorophenyl)-6-morpholino-4*H*-thiopyran-4-one (5l). Mp 186−188 °C. ^1H NMR (500 MHz, $CDCl_3$) δ = 3.42 (t, J = 4.5 Hz, 4H), 3.83 (t, J = 4.5 Hz, 4H), 6.16 (s, 1H), 6.92 (s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H). IR (KBr, cm^{-1}) 1603, 1522, 1372, 1221, 1035, 833. ES-MS (*m/z*) 330.5 $[M + Na]^+$.

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Supporting Information Available: Spectral data for compounds **2b**−**l** and **3cb** and NMR spectra copies of compounds **2a**−**l**, **3ca**−**cb**, **4l**, and **5l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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