Thiophene Systems. 13. The Synthesis of Novel Thienopyranones [1]

James J. McNally, Pauline J. Sanfilippo*, Louis Fitzpatrick and Jeffery B. Press

The R. W. Johnson Pharmaceutical Research Institute,
Raritan, NJ 08869 and Spring House, PA 19477

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The syntheses and spectral properties of novel dimethyl-substituted thieno[3,2-*b*]-, [3,4-*b*]- and [2,3-*b*]pyranones are described. The uv spectra of the three systems are distinctly different as supported by HOMO/LUMO calculations. 5,6-Dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one (**10**) and 5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (**20**) represent the first members of these thienopyranone ring systems.

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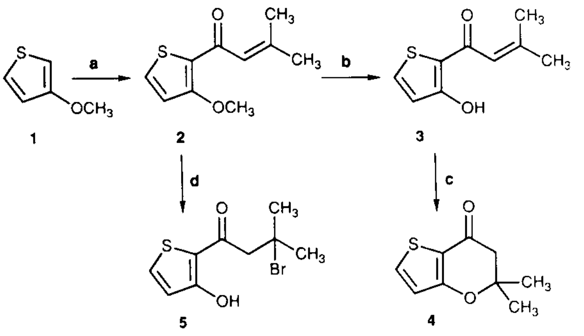
Chroman-4-ones are useful intermediates for the preparation of antiviral, antiallergic, cardiovascular and antisecretory agents [2,3]. One such example is 4′,6-dichloroflavan (BW683C) which is reported to be one of the most potent inhibitors of certain serotypes of rhinovirus [4]. In another vein, thiophene is known to be electronically and sterically similar to benzene [5,6]. The use of thiophene as a bioisosteric replacement for benzene in pharmacologically active compounds has been well documented [7,8]. Our on-going research in the area of thiophene derivatives [1,9,10] led us to a synthetic program directed to thiophene analogues of chroman-4-ones. As noted in previous studies [1,10], the various thiophene isomers produce different and unpredictable pharmacological profiles. Hence, we began a program to prepare all three thiophene regioisomers of the chroman-4-ones. We now report the syntheses of the novel dimethyl-substituted thieno[3,2-*b*]-, [3,4-*b*]- and [2,3-*b*]pyranones.

A 5,6-dihydro-5-aryl-substituted thienopyranone has been reported for the thieno[3,2-*b*]pyran system [11,12]. The synthesis of this derivative utilizes a Friedel-Crafts aroylation of 3-methoxythiophene followed by reaction with pyridinium hydrochloride which both demethylates as well as cyclizes to the final product. Our synthesis of 5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,2-*b*]pyran-7-one (**4**) also uses 3-methoxythiophene (**1**) (Scheme 1) [13]. Friedel-Crafts acylation of **1** with 3,3-dimethylacryloyl chloride in the presence of tin(IV) chloride gives 3-methoxy-2-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**2**). As we have reported previously, tin(IV) chloride provides a superior catalyst for acylation of thiophene derivatives under extremely mild conditions [9]. Attempts to demethylate **2** using protic acids such as hydroiodic acid or hydrobromic acid causes decomposition. Trimethylsilyl iodide reacts with **2** to give a low yield of demethylated product **3** mixed with the desired pyranone **4**. Treatment of **2** with boron tribromide results in demethylation as well as a relatively unexpected hydrobromination of the enone to give **5**. Surprisingly, using acidic or basic conditions, **5** fails to cyclize to **4**. The best method of demethylation of **2** uses boron trichloride to produce **3** in high yield. Ring closure of **3** proceeds smoothly using a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene to give the desired thieno[3,2-*b*]pyran-7-one **4**.

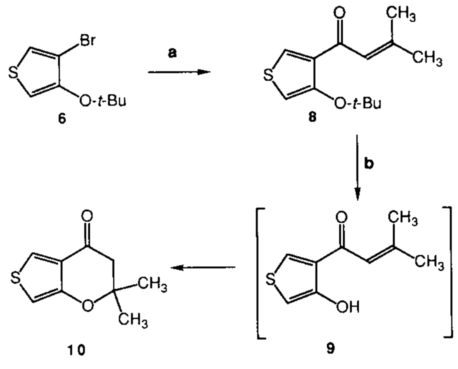
Unlike the synthesis of the thieno[2,3-*b*]pyran-7-one ring system which takes advantage of the strong activation of the 2-position of thiophene towards electrophilic substitution (especially with the 3-methoxy substitutent), the synthesis of the thieno[3,4-*b*]pyran-7-one ring system **10** requires sequential activation of the 3- and 4-positions of thiophene. Halogen exchange with organolithium reagents and subsequent magnesium bromide exchange has been documented for thiophene systems [14,15]. Using this approach on commercially available 3,4-dibromothiophene, reaction with *n*-butyllithium and *t*-butyl perbenzoate produces 4-bromo-3-*t*-butoxythiophene (**6**) (Scheme 2) [14]. A second lithium-halogen exchange with *t*-butyllithium on **6** and subsequent acylation using *N*-methoxy-*N*-methyl-3,3-dimethylacrylamide (**7**) [16] gives 3-*t*-butoxy-4-

Scheme 1



(a) 3,3-dimethylacryloyl chloride, $SnCl_4$ (b) BCl_3 (c) p-TsA (d) BBr_3

Scheme 2

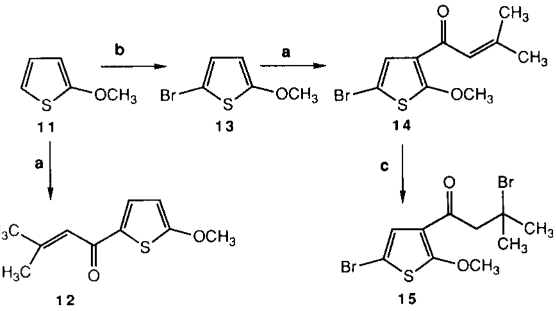


(a) *t*-BuLi, *N*-methoxy-*N*-methyl-3,3-dimethylacrylamide (b) p-TsA

(3-methyl-1-oxo-2-buten-1-yl)thiophene (**8**). Removal of the *t*-butyl group and subsequent ring closure to the thieno[3,4-*b*]pyran-7-one **10** proceeds smoothly in one step with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene. Formation of the intermediate alcohol **9** is observed by thin layer chromatography as well as by ^{1}H nmr, but simultaneous formation of **10** interferes with the isolation or purification of **9**.

The thieno[2,3-*b*]pyran-4-one **20** ring system proved to be the most difficult to prepare. Our first attempt started with commerically available 2-methoxythiophene (**11**) (Scheme 3). Acylation with 3,3-dimethylacryloyl chloride in the presence of tin(IV) chloride gives exclusively 2-methoxy-5-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**12**) as might be expected due to the activation of thiophene in the 2- and 5-positions. To acylate the 3-position of **11** which is required for the thieno[2,3-*b*]pyran system, the 5-position had to be blocked. Bromination of **11** gives **13** and treatment with 3,3-dimethylacryloyl chloride and tin(IV) chloride to give 5-bromo-2-methoxy-3-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**14**). Attempts to demethylate **14** using boron trichloride, trimethylsilyl iodide and pyridinium hydrochloride failed. Treatment of **14** with boron tribromide gives exclusively the non-demethylated hydrobromide product **15** analogous to the formation of **5**. Also analogous to **5**, **15** would not ring-close to **20**.

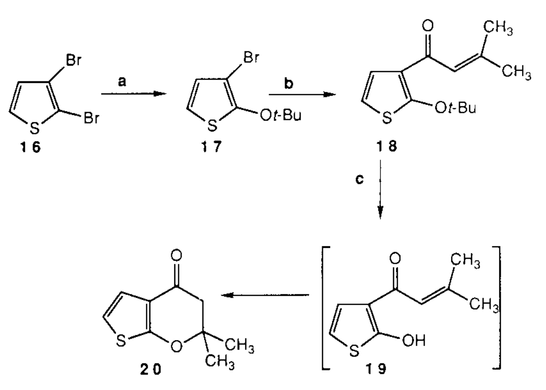
Scheme 3



(a) 3,3-dimethylacryloyl chloride,$SnCl_4$ (b) Br_2 (c) BBr_3

The synthesis of 5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (**20**) is successfully accomplished starting with the commercially available 2,3-dibromothiophene (**16**) (Scheme 4). Generation of the organolithium species using *n*-butyllithium and subsequent reaction with *t*-butyl perbenzoate gives 3-bromo-2-*t*-butoxythiophene (**17**). Lithium-halogen exchange of **17** with *t*-butyllithium followed by reaction with *N*-methoxy-*N*-methyl-3,3-dimethylacrylamide (**7**) gives 2-*t*-butoxy-3-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**18**). Deprotection and ring closure to the thieno[2,3-*b*]pyran-4-one **20** proceeds smoothly using a catalytic amount of *p*-toluenesulfonic acid in toluene, also without the isolation of the intermediate alcohol **19**.

Scheme 4



(a) n-BuLi, $MgBr_2{\cdot}Et_2O$,t-BuO_3CPh
(b) *t*-BuLi,*N*-methoxy-*N*-methyl-3,3-dimethylacrylamide (c) p-TsA

The spectral properties of these novel dimethyl-substituted thieno[3,2-*b*]-, [3,4-*b*]- and [2,3-*b*]pyranones are consistent with the structures of **4**, **10** and **20**. Interestingly, the uv spectra of the three systems are distinctly different with maxima at 308, 263 and 298 nm, respectively. Geometry optimization of the three structures by MNDO [17] indicate that 5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,2-*b*]pyran-7-one (**4**) is the most stable followed by the 5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (**20**). The 5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one (**10**) is the least stable. The energy difference between the least and most stable compounds is 1.66 kcal/mole. Differences were also found in the HOMO/LUMO characteristic of the three molecules which supports the differences in the uv spectra and may indicate possible differences in chemical reactivities.

Both 5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one (**10**) and 5,6-dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (**20**) represent the first members of these thienopyranone ring systems, while 5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,2-*b*]pyran-7-one (**4**) is the first example of a non-arylsubstituted thienopyranone ring system. The use of these derivatives in further chemical studies will be the subject of future reports from our laboratories.

EXPERIMENTAL

Melting point determinations were performed on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ^{1}H nmr were determined relative to TMS in deuteriochloroform on a Bruker WP-100 FT or a GE QE-300 spectrometer. Microanalyses were performed on a Perkin Elmer model 240c elemental analyzer and mass spectra were determined on a Finnigan Mat 8230 using desorption chemical ionization techniques. Silica Gel 60, 230-400 mesh, was used for both flash chromatography and medium pressure chromatography. The uv spectra were measured in ethanol on a Hewlett Packard model 8450A UV/VIS spectrophotometer.

3-Methoxy-2-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**2**).

A solution of 3-methoxythiophene (**1**) [13] (21.3 g, 0.19 mole) in dichloromethane (50 ml) was slowly added to a solution of 3,3-dimethylacryloyl chloride (22 ml, 0.20 mole) and tin(IV) chloride (23 ml, 0.20 mole) in dichloromethane (350 ml) at 0-5°. After stirring for 1 hour, the solution was poured into ice water (1 ℓ). The organic layer was separated, washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo*. The resulting oil was purified by flash chromatography (dichloromethane) to give 29.6 g (81%) of **2**, mp 49-51°; ir (potassium bromide): 1671, 1628, 1430 cm^{-1}; ms: m/z 197 (MH^+); ^1H nmr: δ 1.98 (d, J = 1.2 Hz, 3H), 2.23 (d, J = 1.1 Hz, 3H), 3.98 (s, 3H), 6.85 (d, J = 5.5 Hz, 1H), 6.89 (dd, J = 1.1 Hz, J = 1.2 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H).

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.19; H, 6.17; S, 16.31.

3-Hydroxy-2-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**3**).

A solution of boron trichloride, (1.0 *M* in dichloromethane, 800 ml, 0.80 mole) was added to a solution of **2** (52.3 g, 0.27 mole) in dichloromethane (400 ml) at −10 to 5°. The solution was stirred 1.5 hours at −5° then poured into ice water (1000 ml). The organic layer was separated, dried (sodium sulfate), and eluted through a pad of silica gel. The solvent was evaporated *in vacuo* and the resultant oil was crystallized from hexanes to give 40.0 g (82%) of **3**, mp 32-33°; ir (potassium bromide): 1641, 1581, 1541 cm^{-1}; ms: m/z 183 (MH^+); ^1H nmr: δ 2.00 (d, J = 1.1 Hz, 3H), 2.30 (d, J = 1.0 Hz, 3H), 6.25 (m, 1H), 6.75 (d, J = 5.3 Hz, 1H), 7.37 (d, J = 5.3 Hz, 1H), 12.14 (s, exchanges with deuterium oxide, 1H).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.54; S, 17.59. Found: C, 59.35; H, 5.51; S, 17.62.

5,6-Dihydro-5,5-dimethyl-7*H*-thieno[3,2-*b*]pyran-7-one (**4**).

A solution of **3** (39.0 g, 0.214 mole) and *p*-toluenesulfonic acid (3.5 g, 0.018 mole) in toluene (400 ml) was heated to reflux for 18 hours. The solution was washed with saturated aqueous sodium bicarbonate and dried (sodium sulfate). The solvent was evaporated *in vacuo* to give 38.6 g (99%) of **4**, oil, bp 145 to 155° (0.35 mm Hg); ir (neat): 2979, 1664, 1530 cm^{-1}; ms: m/z 183 (MH^+); ^1H nmr: δ 1.51 (s, 6H), 2.67 (s, 2H), 6.67 (d, J = 5.4 Hz, 1H), 7.60 (d, J = 5.4 Hz, 1H); uv: λ max (log ϵ) 276 (3.97), 308 (3.88) nm.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.54; S, 17.69. Found: C, 59.39; H, 5.53; S, 17.67.

3-Hydroxy-2-(3-bromo-3-methyl-1-butanon-1-yl)thiophene (**5**).

A solution of boron tribromide, (1.0 *M* in dichloromethane, 60 ml, 0.06 mole) was slowly added to a solution of **2** (3.0 g, 0.015 mole) in dichloromethane (50 ml) at 0 to 5°. After stirring for 1 hour, ice water (200 ml) was slowly added to the reaction. The organic layer was separated, washed with water, dried (magnesium sulfate) and eluted through a pad of silica gel. The solvent was evaporated *in vacuo* and the resultant oil was characterized as a 4:1 mixture of **3** and **5**; ^1H nmr: δ 1.99 (s, 6H), 3.32 (s, 2H), 6.77 (d, J = 5.3 Hz, 1H), 7.46 (d, J = 5.3 Hz, 1H), 11.56 (br s, exchanges with deuterium oxide, 1H).

Exact Mass Calcd. for $C_9H_{11}O_2SBr$: 261.9663 u. Found: 261.9682 u.

N-Methoxy-*N*-methyl-3,3-dimethylacrylamide (**7**).

3,3-Dimethylacryloyl chloride (28.2 ml, 0.25 mole) was slowly added to a mixture of *N,O*-dimethylhydroxylamine hydrochloride (27.2 g, 0.28 mole) and triethylamine (75 ml, 0.519 mole) in dichloromethane (300 ml) at 0 to 30° then stirred 1 hour at 0°. The resultant mixture was washed sequentially with 1 *N* hydrochloric acid and 1 *N* sodium hydroxide then dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the residue vacuum distilled (60-70°, 0.2 mm Hg) to give 26.8 g (74%) of **7** as a colorless oil; ir (neat): 2938, 1660 cm^{-1}; ms: m/z 144 (MH^+); ^1H nmr: δ 1.91 (d, J = 1.2 Hz, 3H), 2.14 (d, J = 0.9 Hz, 3H), 3.20 (s, 3H), 3.68 (s, 3H), 6.12 (br s, 1H).

3-*t*-Butoxy-4-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**8**).

t-Butyllithium (1.7 *M* in pentanes, 66 ml, 0.11 mole) was added to a solution of 4-bromo-3-*t*-butoxythiophene (**6**) [14] (12.5 g, 0.053 mole) in diethyl ether (500 ml) at −75°. After stirring for 1 hour, **7** (16.0 g, 0.112 mole) was added to the solution at −75°. The dry ice-acetone bath was removed and the mixture was stirred at ambient temperature overnight. The mixture was washed with 1 *N* hydrochloric acid and dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (5% diethyl ether-pentane) to give 12.3 g (97%) of **8**, oil; ir (neat): 2977, 1655, 1612, 1520, 1470 cm^{-1}; ms: m/z 239 (MH^+); ^1H nmr: δ 1.37 (d, 9H), 1.97 (d, J = 1.1 Hz, 3H), 2.22 (d, J = 1.1 Hz, 3H), 6.56 (d, J = 3.6 Hz, 1H), 6.85 (br s, 1H), 7.86 (d, J = 3.6 Hz, 1H).

5,6-Dihydro-5,5-dimethyl-7*H*-thieno[3,4-*b*]pyran-7-one (**10**).

A solution of **8** (12.2 g, 0.051 mole) and *p*-toluenesulfonic acid (0.5 g) in toluene (300 ml) was heated to reflux for 2 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (25% hexane-dichloromethane) to give 5.9 g (63%) of **10**, mp 42-45°; ir (neat): 2977, 1692, 1554 cm^{-1}; ms: m/z 183 (MH^+); ^1H nmr: δ 1.44 (s, 6H), 2.62 (s, 2H), 6.43 (d, J = 3.3 Hz, 1H), 8.00 (d, J = 3.3 Hz, 1H); uv: λ max (log ϵ) 217 (3.95), 263 (3.97) nm.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.54. Found: C, 59.40; H, 5.58.

2-Methoxy-5-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**12**).

A solution of **11** (1.0 g, 0.019 mole) in dichloromethane (10 ml) was added to a solution of 3,3-dimethylacryloyl chloride (1.0 ml, 0.087 mole) and tin(IV) chloride (1.0 ml, 0.087 mole) in dichloromethane (10 ml) at 0-5°. After stirring for 1 hour, the solution was poured into ice water (1 ℓ). The organic layer was separated, washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo*. The resulting solid was recrystallized from dichloromethane-hexanes to give 0.60 g (33%) of **12**, mp 59-60°; ms: m/z 197 (MH^+); ^1H nmr: δ 1.97 (s, 3H), 2.22 (s, 3H), 3.95 (s, 3H), 6.22 (d, J = 4.3 Hz, 1H), 6.56 (s, 1H), 7.42 (d, J = 4.3 Hz, 1H).

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34. Found: C, 60.85; H, 5.91; S, 16.24.

5-Bromo-2-methoxy-3-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**14**).

A solution of 2-methoxythiophene (5.2 g, 0.046 mole) in diethyl ether (50 ml) at 0° was treated dropwise with bromine (2.3 ml, 0.046 mole). After stirring for 2 hours, the solution was poured into ice cold aqueous saturated sodium bicarbonate (50 ml). The mixture was extracted with diethyl ether (50 ml) and the organic layer was dried (sodium sulfate). The solvent was evaporated *in vacuo* to give 8.0 g (90%) of 5-bromo-2-methoxythiophene (**13**) which was taken on without further purification.

A solution of **13** (8.0 g, 0.042 mole) in dichloromethane (100 ml) was added to a solution of 3,3-dimethylacryloyl chloride (4.6 ml, 0.042 mole) and tin(IV) chloride (4.9 ml, 0.042 mole) in dichloromethane (100 ml) at 0-5°. After stirring for 1 hour, the solution was poured into ice water (1000 ml). The organic layer was separated, washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo*. The resulting solid was recrystallized from dichloromethane-hexanes to give 5.3 g (46%) of **14**, mp 102-103°; ir (potassium bromide): 1647, 1608 cm^{-1}; ms: m/z 275 (M^+) (1 Br); ^1H nmr: δ 1.99 (s, 3H), 2.24 (s, 3H), 4.06 (s, 3H), 6.53 (s, 1H), 7.45 (s, 1H).

Anal. Calcd. for $C_{10}H_{11}BrO_2S$: C, 43.65; H, 4.03; S, 11.65. Found: C, 43.81; H, 3.66; S, 11.69.

5-Bromo-3-(3-bromo-3-methyl-1-butanon-1-yl)-2-methoxythiophene (**15**).

This compound was obtained as an amber oil from the reaction of **14** with boron tribromide as described in the preparation of **5**; ms: m/z 356 (M^+), (2 Br); ^1H nmr: δ 1.99 (s, 6H), 3.32 (s, 2H), 4.00 (s, 3H), 7.46 (s, 1H).

Exact Mass Calcd. for $C_{10}H_{12}Br_2O_2S$: 353.8926 u. Found: 353.8944 u.

3-Bromo-2-*t*-butoxythiophene (**17**).

A solution of **16** (10.0 g, 0.041 mole) in diethyl ether (150 ml) at −78° was treated with *n*-butyllithium (2.5 *M*, 20.0 ml, 0.050 mole) over a period of 20 minutes. The mixture was stirred at −78° for 1 hour. Magnesium bromide etherate, (13.0 g, 0.050 mole) was added as a solid in two portions, 15 minutes apart. The mixture was stirred at −78° for 1 hour and then at room temperature for 2 hours. The mixture was cooled to 0° and *t*-butyl perbenzoate (9.2 g, 0.047 mole) was added, maintaining the reaction temperature between 0-5°. The mixture was stirred at room temperature overnight then quenched with ice (100 g) and ice cold 2 *N* hydrochloric acid (25 ml). The organic layer was separated and washed with cold 1 *N* sodium hydroxide, water, (until neutral), and brine. The organic layer was concentrated *in vacuo* and the residue was purified by flash chromatography (pentane) to yield 6.0 g, (62%), of **17** as a pale oil; ms: m/z 236 (MH^+); ^1H nmr: δ 1.43 (s, 9H), 6.76 (s, 2H).

2-*t*-Butoxy-3-(3-methyl-1-oxo-2-buten-1-yl)thiophene (**18**).

A solution of **17** (4.0 g, 0.017 mole) in diethyl ether (75 ml) at −78° was treated with *t*-butyllithium (1.7 *M*, 25 ml, 0.042 mole) over a period of 20 minutes. After stirring for 1.5 hours, the solution was treated with **7** (3.0 g, 0.021 mole) over a period of 20 minutes. The mixture was stirred at room temperature overnight then quenched with ice cold 1 *N* hydrochloric acid (100 ml). The organic layer was separated then washed with ice cold water, brine and dried (sodium sulfate). The organic layer was concentrated *in vacuo* and the resulting oil was purified by mplc chromatography (3% diethyl ether-pentane) to yield 2.5 g (61%) of **18**, oil; ms: m/z 239 (MH^+); ^1H nmr: δ 1.44 (s, 9H), 1.96 (s, 3H), 2.19 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.87 (s, 1H), 7.22 (d, J = 6.4 Hz, 1H).

5,6-Dihydro-6,6-dimethyl-4*H*-thieno[2,3-*b*]pyran-4-one (**20**).

A solution of **18** (2.5 g, 0.011 mole) in toluene (50 ml) and *p*-toluenesulfonic acid (0.10 g) was heated to reflux for 4 hours. The mixture was washed with saturated sodium bicarbonate, brine and dried (sodium sulfate). The resulting oil was purified by flash chromatography (dichloromethane) to give 1.1 g (58%) of **20**, oil; ms: m/z 183 (MH^+); ^1H nmr: δ 1.53 (s, 6H), 2.62 (s, 2H), 6.46 (d, J = 6.1 Hz, 1H), 7.05 (d, J = 6.1 Hz, 1H); uv: λ max (log ϵ) 230 (4.19), 249 (3.84), 298 (3.54) nm.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.33; H, 5.67.

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