Benzylidene–Thiolactone Rearrangement: Synthesis and Rearrangement of 5-Substituted 3-Benzylidene-4-thiolen-2-ones[1]

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Condensation of 5-substituted 4-thiolen-2-ones (1) with aromatic aldehydes (2) in anhydrous ethanolic HCl generates the 3-benzylidene derivatives 3. These can be rearranged in base (benzylidene–thiolactone rearrangement) to 2,5-disubstituted thiophene-3-carboxylic acids (4, 5, or 6).

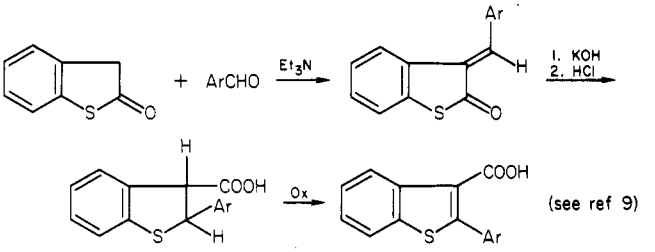
Earlier publications from these laboratories have reported two related transformations: the salicylidene–thiolactone[2-7] and the benzylidene–thiolactone rearrangements.[8,9] To date the benzylidene–thiolactone rearrangement has been applied only to aromatic aldehydes and thianaphthen-2-one.[8,9] With an amine base as a catalyst, excellent yield of the benzylidenethianaphthen-2-ones were obtained which rearranged to 2-aryl-2,3-dihydrothianaphthene-3-carboxylic acids. These could be oxidized under mild conditions to the fully aromatic 2-arylthianaphthene-3-carboxylic acids (Scheme I).

One limitation to extending the reaction to nonbenzenoid systems has been the difficulty of preparing such benzylidenes of thiobutyrolactones or 4-thiolen-2-ones. Thianaphthen-2-one possesses a special activating factor in the potential aromaticity of its enolate which no doubt contributes to its facile condensation propensity.[9] Lucast and Wemple prepared a labile, polymerization-prone α-methylene-γ-thiobutyrolactone by a three-step, base-promoted reaction of formaldehyde with thiobutyrolactone.[10] Zimmer used a Wittig technique on a β-bromothiobutyrolactone to produce an arylidene,[11] and Rioult employed sodium *tert*-amylate to catalyze arylidene formation between benzaldehydes and a methylated γ-thiobutyrolactone.[12]

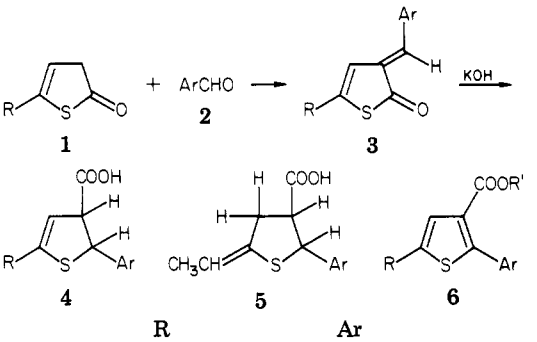
No simple, direct method exists to form arylidenes of unsubstituted thiobutyrolactones, but we have found that 4-thiolen-2-ones (1) can be condensed under acidic conditions at ice-bath temperatures with benzaldehydes (2) to give 32–86% yields of the 3-arylidene-4-thiolen-2-ones (3, Scheme II). The 5-aryl-4-thiolen-2-ones (1, R = Ar) were prepared by sulfuration and cyclization of β-aroylpropionic acids.[13] These thiolactones readily air oxidized to thioindigoid dimers especially upon contact with base. Blue contaminants in the products could be avoided by performing the condensation in anhydrous medium, at ice-bath temperatures, and introducing a steady stream of dry HCl under the surface of the solution. In an alternative method the labile 5-aryl-4-thiolen-2-one can be trapped in situ with the aromatic aldehyde to generate the benzylidene directly.[14] In one case (Scheme III), **3c** was prepared in 19% from β-benzoylpropionic acid and 4-chlorobenzaldehyde vs 9% by the method which requires isolation of 5-phenyl-4-thiolen-2-one and subsequent condensation with the aldehyde.

5-Ethyl-4-thiolen-2-one (1, R = Et) was prepared by Hornfeldt's method via the thienyl boronic acid by oxi-

Scheme I

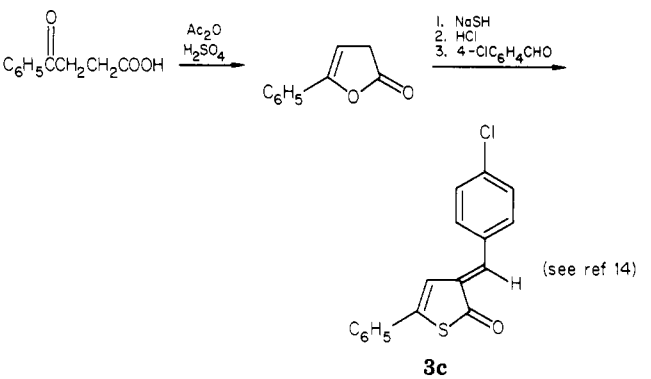


Scheme II



	R	Ar
a	4-$CH_3C_6H_4$	C_6H_5
b	4-$CH_3C_6H_4$	3-CH_3O-4-OHC_6H_3
c	C_6H_5	4-ClC_6H_4
d	CH_3CH_2	4-ClC_6H_4
e	CH_3CH_2	3,4-(-OCH_2O-)C_6H_3

Scheme III



3c

5-Ethyl-4-thiolen-2-one (1, R = Et) was prepared by Hornfeldt's method via the thienyl boronic acid by oxi-

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Table I. 5-Substituted 3-Arylidene-4-thiolen-2-ones[a]

compd	R	Ar	mp, °C	yield, %	solvent: ^{1}H NMR δ	IR,[c] cm^{-1}
3a	4-$CH_3C_6H_4$	C_6H_5	119-120	46	acetone-d_6: 2.38 (s, 3 H), 7.14-8.02 (m, 11 H)	1680
3b	4-$CH_3C_6H_4$	3-CH_3O-4-OHC_6H_3	165-166	35	acetone-d_6: 2.36 (s, 3 H), 3.98 (s, 3 H), 6.90-7.75 (m, 9 H), 8.48 (s, 1 H)	1655
3c	C_6H_5	4-ClC_6H_4	166-168	76[d]	$CDCl_3$: 7.30-8.00 (m, 11 H)	1675
3d	C_2H_5	4-ClC_6H_4	67-68	32	$CDCl_3$: 1.25 (t, 3 H, J = 8 Hz), 2.62 (q, 2 H, J = 8 Hz), 6.62 (s, 1 H), 7.26 (s, 1 H), 7.48 (br s, 4 H)	1675
3e	C_2H_5	3,4-(-OCH_2O-)C_6H_3	99-102[b]	86	$CDCl_3$: 1.23 (t, 3 H, J = 8 Hz), 2.58 (q, 2 H, J = 8 Hz), 6.00 (s, 2 H), 6.50-7.25 (m, 5 H)	1665

[a] Satisfactory analytical data (±0.35% for C and H) were reported for all compounds. [b] Lit.[15] mp 80-82 °C. [c] Spectra obtained in hydrocarbon mulls. [d] An alternative synthesis, in higher overall yield, has been reported.[14]

dation with peroxide.[15] Isomerization to the conjugated 5-ethyl-3-thiolen-2-one, which does not undergo the benzylidene formation, can occur if the oxidation reaction temperature is not held below 0 °C.[16]

Rearrangements of the benzylidenes **3a–e** with KOH and methanol proceeded smoothly with the 5-ethyl-4-thiolen-2-one adducts (**3d** and **3e**), yielding the expected dihydrothiophene carboxylic acids with endocyclic and exocyclic unsaturation (i.e., **4d/5d** and **4e/5e**) in yields of 44% and 33%, respectively. The relative percentages of each isomer in the isolated mixtures were readily determined from the NMR integration of the respective proton resonances. No trace of oxidative dehydrogenation was detected.

Rearrangement of **3a** and **3c**, however, gave the respective aromatized 2,5-diaryl-3-carboxythiophenes (**6a** and **6c**). The free carboxylic acid could not be obtained in analytical purity from rearrangement of **3a**, and the methyl ester was isolated instead by post-rearrangement in situ esterification. The more facile oxidation in the rearrangement of **3a** and **3c** no doubt reflects the greater resonance gain occasioned by the presence of 5-aryl moiety.

Compound **3b** resisted rearrangement completely and either generated the potassium phenolate of the starting material, upon treatment with methanolic KOH, or underwent a reverse aldol cleavage to vanillin. Not only is the thiolactone carbonyl in **3b** of diminished reactivity, a fact reflected in the lower C=O stretch (Table I), but the phenolate salt produced in the methanolic caustic also further reduces the electrophilicity of the thiolactone carbonyl.

The benzylidene thiolactone rearrangement does, however, provide a new synthetic entry to 3-carboxythiophenes and extends the generality of the reaction to nonbenzenoid thiolactone reactants.

Experimental Section

Melting points were obtained in capillaries in a Thomas-Hoover apparatus and are reported uncorrected. IR spectra were obtained as hydrocarbon mulls on a Perkin-Elmer Model 257. Mass spectra were provided by Dr. James Sturm and William Anderson of the Lehigh University Mass Spectrometry Laboratory and were obtained on a Hitachi RMU-6E double-focusing spectrometer and on a Finnigan Model 4000 mass spectrometer with an INCOS data system. ^{1}H NMR spectra were obtained on a Hitachi R20A and on a JEOL FX90Q spectrometer. The Robertson Microanalytical Laboratory of Florham Park, NJ, provided the combustion analyses.

Preparation of 5-Substituted 3-Arylidene-4-thiolen-2-ones (3a–e). General Method. An equimolar (5.75 mmol) solution of the requisite 5-substituted 4-thiolen-2-ones[4,5] (e.g., **1a–c**) and the corresponding benzaldehydes (**2**) was prepared in 50 mL of absolute ethanol, chilled in an ice–water bath, and stirred vigorously while anhydrous HCl gas was introduced under the surface of a gas bubbler. After 5 min of exposure the gas flow was terminated, and the contents of the flask were stirred in an ice bath for an additional 3 h and allowed to stand at 0 °C for 1 h to complete precipitation. The product was removed by filtration, and additional material was isolated from the concentrated mother liquor. The analytical samples were obtained by recrystallization from 1:1 ethyl ether/petroleum ether (bp 60–110 °C). Yields and physical properties are reported in Table I.

Rearrangement of 5-Substituted 3-Arylidene-4-thiolen-2-ones. A solution of 2 mmol of the arylidene (**3a–e**) in 40 mL of refluxing methanol was treated with the dropwise addition of 4 mmol of potassium hydroxide prepared as a 10% solution in methanol. In all cases the color of the solution deepened to an intense orange or red. The mixture was evaporated to virtual dryness and then chilled in an ice bath. Solid or semisolid pastes were obtained whose infrared spectra displayed intense absorptions at ca. 1585 cm^{-1} (COO^-); an exception was noted in the reaction of **3b** where broad C=O absorption was observed at 1635 cm^{-1}. These residues were dissolved in a minimum amount of water (ca. 15 mL), neutralized with 10% aqueous hydrochloric acid, and extracted with two 25-mL portions of $CHCl_3$. The dried ($MgSO_4$) chloroform layers were concentrated in vacuo, and the products were isolated by chilling in an ice bath. Analytical material was obtained by a single recrystallization from the indicated solvent(s).

Compound (**6a**, R′ = CH_3) was isolated as its methyl ester, from the crude acid precursor which could not be adequately purified, by refluxing the acid in anhydrous methanol containing 1% *p*-toluenesulfonic acid for 4 hours.

6a (R′ = CH_3): 24% yield (from methanol); mp 95–97 °C; IR (Nujol) 1715 cm^{-1} (CO); NMR ($CDCl_3$) δ 2.29 (s, 3, CH_3) 3.75 (s, 3, CH_3O), 7.2–7.7 (m, 10, Ar H); mass spectrum, m/e 308 (M^+), 293 ($M^+ - CH_3$), 277 ($M^+ - CH_3O$), 248 ($M^+ - COOCH_3$). Anal. Calcd for $C_{19}H_{16}SO_2$: C, 73.98; H, 5.23; S, 10.38. Found: C, 73.59; H, 5.33; S, 10.50.

6c (R′ = H): 48% yield (from 1:1 ethanol/water); mp 268–270 °C; IR (Nujol) 3400–2500 (br, OH), 1690 cm^{-1} (CO); NMR (acetone-d_6) δ 7.3–7.9 (m, Ar H); mass spectrum, m/e 314 (M^+), 270 ($M^+ - CO_2$). Anal. Calcd for $C_{17}H_{11}ClSO_2$: C, 64.88; H, 3.52; S, 10.16. Found: C, 65.05; H, 3.61; S, 10.16.

4d and **5d** (R′ = H): 44% yield of mixed isomers (from 1:1 ethanol/water); mp 103–106 °C; IR (Nujol) 3500–2500 (br, OH), 1700 cm^{-1} (CO); NMR ($CDCl_3$) for **4d** (>90% of mixture) δ 1.13 (t, 3, J = 8 Hz, CH_2CH_3), 2.30 (q, 2, J = 8 Hz, CH_2CH_3), 3.95 (m, 1, C_3 H), 5.18 (m, 2, C_2 H and C_4 H), 7.1–7.4 (q, 4, Ar H), 10.5 (br s, 1, exchangeable, COOH); NMR ($CDCl_3$) for **5d** (<10% of mixture) δ 1.60 (d, 3, $=CHCH_3$), 2.6–2.8 (m, 3, C_3 H and C_4 H_2), 4.80 (d, 1, C_2 H), 5.50 (m, 1, $CHCH_3$), aromatic and carboxyl protons isochronous with those in **4d**. Anal. Calcd for $C_{13}H_{13}ClSO_2$: C, 58.11; H, 4.87; S, 11.91. Found: C, 58.13; H, 5.00; S, 12.22.

4e and **5e** (R′ = H): 33% yield of mixed isomers (from 1:1 ethanol/water); mp 101–104 °C; IR (Nujol) 3450–2600 (br, OH), 1705 cm^{-1} (CO); NMR ($CDCl_3$) for **4e** (45% of mixture) δ 1.15 (t, 3, J = 8 Hz, CH_2CH_3), 2.28 (q, 2, J = 8 Hz, CH_2CH_3), 4.05 (m, 1, C_3 H), 5.20 (m, 23, C_2 H and C_4 H), 5.90 (s, 2, OCH_2O), 6.50–7.00

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(m, 3, Ar H), 9.90 (br s, 1, exchangeable COOH); NMR ($CDCl_3$) for **5e** (55% of mixture) δ 1.63 (d, 3, J = 8 Hz, $=CHCH_3$), 2.85–3.25 (m, 3, C_3 H and C_4 H_2), 4.85 (d, 1, J = 9 Hz, C_2 H), 5.45 (q, 1, J = 8 Hz, $=CHCH_3$), 5.90 (s, 2, OCH_2O), aromatic and carboxylic resonances isochronous with those in **4e**. Anal. Calcd for $C_{14}H_{14}SO_4$: C, 60.35; H, 5.07; S, 11.52. Found: C, 60.06; H, 5.21; S, 11.33.

Attempted Rearrangement of 3b. When **3b** was treated as described above, the blood-red methanolic caustic solution yielded upon concentration a purple solid (mp >360 °C) which left a residue upon ignition and displayed a violet potassium-like flame upon combustion on a platinum wire. It was identified as the salt of **3b**, IR (Nujol) 1635 cm^{-1}. Anal. Calcd for $C_{19}H_{15}SO_3K$: C, 62.96; H, 4.17. Found: C, 62.88; H, 4.19.

Acidification with 20 mL of 10% hydrochloric acid returned **3b** which was identified by melting point, mixture melting point, and infrared spectral comparison with starting material.

The rearrangement was repeated with 2 mmol of **3b** suspended in 25 mL of anhydrous methanol and refluxed for 6 h with 4 mmol of potassium hydroxide as a 10% solution in methanol. After 6 h the blood-red color still remained, and the reaction mixture was allowed to stand for 1 week at room temperature. The red color faded to a pale yellow. Upon concentration in vacuo and chilling in an ice–salt bath, 192 mg (62%) of pale yellow needles (mp 78–81 °C) were obtained whose infrared spectrum, ^1H NMR spectrum, and undepressed mixture melting point with authentic material confirmed the identification of vanillin.

Registry No. **1a**, 61477-86-9; **1c**, 939-09-3; **1d**, 56761-31-0; **2a**, 100-52-7; **2b**, 121-33-5; **2c**, 104-88-1; **2e**, 120-57-0; **3a**, 86239-17-0; **3b**, 86239-18-1; **3b**·K, 86239-27-2; **3c**, 80224-53-9; **3d**, 86239-19-2; **3e**, 86239-20-5; **4d**, 86239-23-8; **4e**, 86239-25-0; **5d**, 86239-24-9; **5e**, 86239-26-1; **6a** (R′ = H), 86239-21-6; **6a** (R′ = CH_3), 67139-62-2; **6c** (R′ = H), 86239-22-7; vanillin, 121-33-5.

Reaction of 3,4-Bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-Oxide with Olefins

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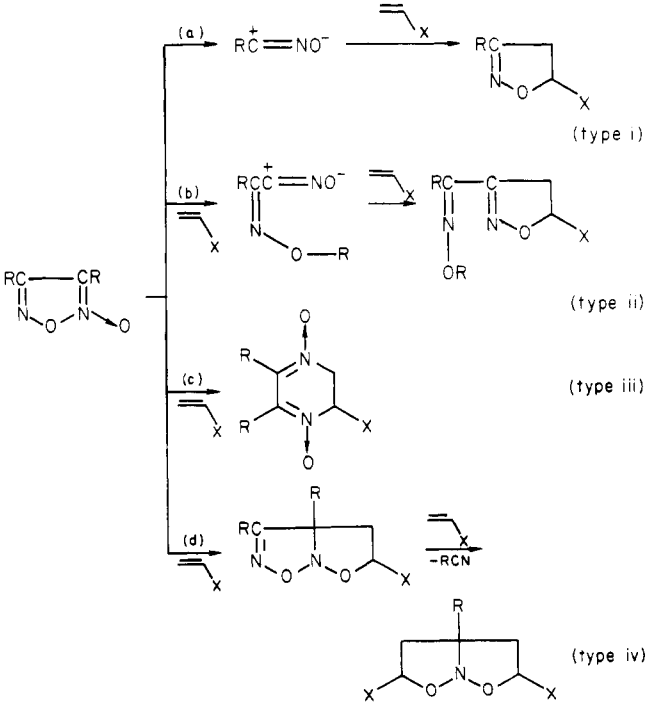
3,4-Bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide (1) has been shown to react with several olefins in a molar ratio of 1:2, giving 5-(ethoxycarbonyl)-1-aza-2,8-dioxabicyclo[3.3.0]octanes (2). Evidence is presented that these products arise from 1,3-dipolar cycloaddition, elimination of ethyl cyanoformate from the initial cycloadducts, and 1,3-dipolar cycloaddition of the resulting isoxazoline *N*-oxides with another mole of olefin.

Extensive studies have been carried out on the syntheses and the reaction of 1,2,5-oxadiazole 2-oxides (furoxans).[1] While it is known that furoxans are relatively stable compounds, three types of reaction with olefins can occur under relatively drastic conditions (Scheme I). Some sterically hindered furoxans[2] are decomposed thermally to 2 mol of nitrile oxides, which undergo 1,3-dipolar cycloaddition with olefins (C–C bond fission of the oxadiazole ring) (type i). Alternatively, N–O bond fission of the oxadiazole ring with concomitant migration of hydrogen[3] or acyl group[4] gives a nitrile oxide (type ii). Also documented is the conversion of benzofuroxan derivatives to olefin [4 + 2]-cycloadducts (type iii).[5]

Furoxans are formally cyclic 1,3-dipolar nitrones, but nitrone-type 1,3-dipolar cycloaddition reactions with olefins

Scheme I



as shown in Scheme I have not been reported so far (type iv).[6] We report here the first example of a nitrone-type reaction involving 3,4-bis(ethoxycarbonyl)-1,2,5-oxadiazole

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