Improved Synthesis of 3-Aralkylidine-5-arylthiophen-2-(3*H*)ones

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3-Aralkylidene-5-arylthiophen-2-(3*H*)ones can be prepared in two steps from 4-aryl-4-oxobutanoic acids through the intermediacy of butenolides and thiophenones generated by the sequential action of acetic anhydride, sodium hydrosulfide and aromatic aldehydes.

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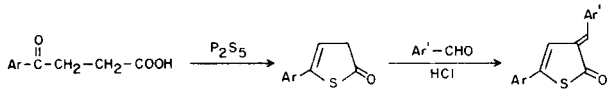
Previous studies in these laboratories with rearrangements of 3-aralkylidine-5-arylthiophene-2-(3*H*)ones (1) utilized a known synthetic technique for the required compounds. As illustrated in Scheme 1, the method of Kosak (2) was used to prepare the corresponding 5-arylthiophen-2-(3*H*)ones, which were then condensed with aromatic aldehydes, the aralkylidene products being utilized in rearrangement studies (1).

Scheme 1



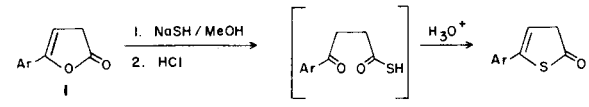
Several factors make this method inconvenient. Of especial importance to the success of the first step are the rigorous exclusion of oxygen (1,2) and the use of fresh phosphorus pentasulfide. In addition, a rather tedious isolation procedure, including extraction with large quantities of chloroform, produces low yields of still-impure (and very air-sensitive) thiolactone. Finally, the thiolactone requires storage under an inert atmosphere because of its labile nature.

Rao and Filler (3) reported an alternative synthesis for the thiolactones desired. This involved the reaction of thiolacetic acid with the corresponding lactones or butenolides, the oxygen undergoing replacement with sulfur. We found this method very variable in yield and unsatisfactory for routine use. The general approach of converting butenolides to thiolactones was, however, an attractive possibility.

While butenolides are not as prone to air-oxidation as the corresponding thiolactones, their usual method of preparation involves cyclization of a β-aroylpropionic acid in refluxing acetic anhydride (4), under which conditions air-oxidation occurs, producing a Pechmann dye (5) as a stubborn contaminant. The mixed acetic anhydride and sulfuric acid cyclodehydration suggested by Kohler and Jansen (6) and the published purification method for the starting β-ketoacids (7) has generated butenolides in high and reproducible yields.

Since carbothioic acids can be obtained from phenyl esters of carboxylic acids by the action of alcoholic sodium hydrosulfide (8-10) we undertook the direct conversion of butenolides to thiolactones (Scheme 2). No attempt was made to exclude oxygen. We were unable to isolate pure

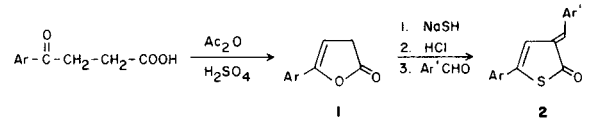
Scheme 2



thiolactones from the medium although the color transformation strongly hinted at the product's presence. The medium was blue-tinted, reminiscent of the blue sulfur-containing oxidation products we had earlier observed from thiolactones, and not the reddish color of the traditional Pechmann dyes. Since the aralkylidene derivatives were the products being sought, we intercepted the labile thiolactones by trapping them *in situ* following the addition of the aromatic aldehydes.

An immediate precipitate of the sparingly-soluble aldol condensation product formed in the medium and it was filtered and purified by recrystallization from 95% ethanol. Although the overall yields of **2a** and **2b** are 26% and 12%, this represents approximately a three-fold increase in yield over that obtained when one attempts to isolate the thiolactones by Kosak's method (2). This complete transformation [**1** to **2**, see Scheme 3] can be carried

Scheme 3



a Ar = Ph (Ar' = p-ClC$_6$H$_4$–)
b Ar = 3,4-diCH$_3$–C$_6$H$_3$ (Ar' = 2,4-diCl–C$_6$H$_3$–)

out in a single reaction vessel.

Of the numerous advantages offered by the method, the most substantial is probably that storage of the butenolide requires no special care, so that its preparation constitutes a convenient stopping point in the synthetic scheme. Finally the ability to isolate their respective aldol products directly suggests that the labile thiolactones may be employed as reactive intermediates without isolation.

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EXPERIMENTAL

Melting points were determined in capillaries on a Thomas-Hoover apparatus and are reported uncorrected. Nmr spectra were determined on a Perkin-Elmer Hitachi R20A Spectrometer with chemical shifts reported on the δ scale relative to TMS. Microanalyses were performed by Dr. G. I. Robertson, Florham Park, N. J.

5-Phenylfuran-2-(3*H*)one (**1a**).

Kohler's and Jansen's cyclodehydration method (6) was extended to the preparation of this butenolide whose earlier synthesis was much less satisfactory. 4-Phenyl-4-oxobutanoic acid was dissolved in dilute sodium hydroxide solution, warmed with charcoal, filtered, reprecipitated with dilute hydrochloric acid and vacuum dried. This purified acid (5.0 g) was suspended in 10 ml of acetic anhydride and treated to the addition of 5 drops of concentrated sulfuric acid whereupon a clear solution resulted. This medium was stirred for 30 minutes during which time the product began to precipitate.

The mixture was added with vigorous stirring to 250 ml of cold water, chilled in an ice bath for 30 minutes, filtered, and the solid washed with 75 ml of water. Recrystallization from 95% ethanol yielded 3.2 g (71%) of the title compound, mp 92-94° (lit mp 91-92°) (4).

5-(3,4-Dimethylphenyl)furan-2-(3*H*)one (**1b**).

4-(3,4-Dimethylphenyl)-4-oxobutanoic acid was purified by the method described (7). The acid (8.2 g) was suspended in 30 ml of acetic anhydride while 18 drops of concentrated sulfuric acid were slowly added. After 15 minutes of stirring, the mixture was added to 500 ml of water and stirred for several minutes.

Following 30 minutes of chilling, a crude pink product was collected on a filter and washed with 100 ml of water. The product was recrystallized from 95% ethanol to yield 4.7 g (63%) of peach-colored needles, mp 112-115.5°, sufficiently pure for the subsequent synthetic step. (A second recrystallization from carbon tetrachloride provided pale-pink needles, mp 113.5-115.5, of analytically pure material; nmr (deuteriochloroform): δ 2.25 (s, 6H, CH_3), 3.31 (d, 2H, CH_2); 5.64 (t, 1H, ArC=CH), 7.0-7.4 (m, 3H, ArH); ir (nujol mull): 1785 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.51.

3-(4-Chlorobenzylidene)-5-phenylthiophen-2-(3*H*)one (**2a**).

A sodium methoxide solution was prepared from 0.8 g of sodium and 40 ml of methanol. This was treated to an addition of hydrogen sulfide, bubbled in at a moderately rapid rate over 15 minutes. To the resulting solution was added 2.1 g of **1a**, after which it was refluxed with stirring for 10 minutes.

Concentrated hydrochloric acid (7.5 ml) was added, followed by a solution of *p*-chlorobenzaldehyde (1.8 g) in methanol (20 ml), and the heating under reflux was resumed for a further 20 minutes. The reaction mixture was subsequently poured into 150 ml of water and stirred for several minutes.

By means of suction filtration and subsequent recrystallization from 200 ml of 95% ethanol, 1.0 g (26%) of bright-yellow needles, mp 166-168°, were procured; ir (nujol mull): 1675 cm^{-1}; nmr (1/1 deuteriochloroform and DMSO-d_6): δ 7.30-8.00 (m, 11, all H's).

Anal. Calcd. for $C_{17}H_{12}O_2S$: C, 72.80; H, 4.31. Found: C, 73.01; H, 4.57.

3-(2,4-Dichlorobenzylidene)-5-(3,4-dimethylphenyl)thiophen-2-(3*H*)one (**2b**).

Sodium metal (1.2 g) was dissolved in 60 ml of methanol. Hydrogen sulfide was introduced for 20 minutes at a rapid rate, after which the butenolide (**1b**, 3.8 g) was added with stirring.

Following a 10 minute reflux, and subsequent acidification with 10 ml of concentrated hydrochloric acid, a solution of 3.5 g of 2,4-dichlorobenzaldehyde in 40 ml of methanol was added, followed by a 20 minute reflux. The reaction mixture was subsequently chilled, after which, the crude solid was isolated by suction-filtration, stirred with water, and refiltered. Upon recrystallization from 95% ethanol, 1.0 g (12%) of a dull-yellow powder. The still-impure substance melted with darkening over the range 170-175°. Recrystallization from methanol improved the purity to yield yellow-orange needles, mp 171.5-173°; nmr (deuteriochloroform): δ 2.29 (s, 6H, CH_3), 7.00 (s, 1H, ArC=CH), 7.1-7.7 (m, 7H, ArH, CH=CCO); ir (nujol mull): 1690 cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}Cl_2OS$: C, 63.17; H, 3.91. Found: C, 63.35; H, 4.05.

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REFERENCES

(1) N. D. Heindel, J. A. Minatelli and D. Harris, *J. Org. Chem.*, **42**, 1465 (1977).

(2) A. I. Kosak, P. J. F. Palchak, W. A. Steele and C. M. Selwitz, *J. Am. Chem. Soc.*, **76**, 4450 (1954).

(3) Y. S. Rao and R. Filler, *J. Heterocyclic Chem.*, **1**, 210 (1964).

(4) R. Fittig and M. Ginsberg, *Ann. Chem.*, **299**, 11 (1898).

(5) E. Klingsberg, *Chem. Rev.*, **54**, 59 (1954).

(6) E. P. Kohler and J. E. Jansen, *J. Am. Chem. Soc.*, **60**, 2142 (1938).

(7) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 81.

(8) R. Seifert, *J. Prakt. Chem.*, **31**, 462 (1885).

(9) P. Weselsky *Ber.*, **2**, 518 (1869).

(10) V. Auger, *Compt. Rend.*, **139**, 798 (1904).