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ORGANIC SYNTHESIS WITH α-CHLOROSULPHIDES. CONVERSION OF PHENOLS INTO γ-LACTONES USING METHYL-2-CHLORO-2-(ALKYL OR ARYLTHIO)CARBOXYLATES

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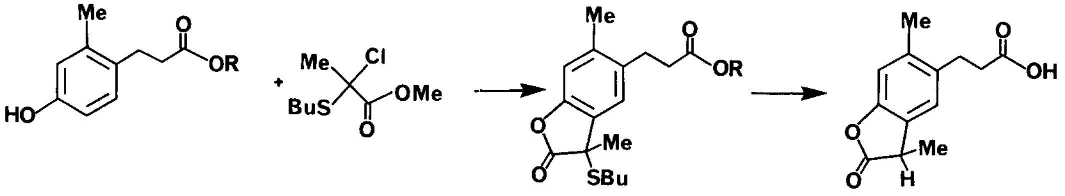
Summary Aromatic γ-lactones can be synthesised from 4-substituted phenols in a single step by zinc chloride-catalysed alkylation with methyl-2-chloro-2-(butylthio or phenylthio)propionate or acetate.

Recent work has established that α-chloroalkyl sulphides are useful electrophiles for alkylation of aromatics[1,2], alkenes[3], alkynes[4], silyl enol ethers[5] and ketene (bis-trimethylsilyl)acetals[6], and in the preceding paper we have shown that they are also readily transformed into a wide variety of (phenylthio)acetals[7,8]. In connection with a problem in sesquiterpene synthesis we required a method of transforming phenolic acid (1) into the γ-lactone (4). A quick solution to the problem was forthcoming when we examined the reaction of (1) with methyl-2-chloro-(butylthio)·propionate (2)[2] in the presence of Lewis acids. The reaction has proved to be quite general for phenols bearing para substitution, offering a convenient route to aromatic γ-lactones. Although zinc chloride and stannic chloride were both efficacious catalysts, the latter was less satisfactory in practice due to its tendency to promote side reactions.

Addition of (2) (.017 mol) to a 1:1 dichloromethane:nitromethane solution of (1) (.016 mol) and anhydrous zinc chloride (.032 mol) at room temperature (reaction time ca. 1 h) gave the sulphenylated lactone (3) in 44% yield[9]. Desulphurisation of (3) with zinc dust in glacial acetic acid furnished the desired lactone (4)[9], m.p. 150-152°C, in essentially quantitative yield. The lactonisation step was much more efficient with the methyl ester rather than the free carboxylic acid, (5) furnishing (6) in 70% yield. Whilst examining the scope of the reaction we found that



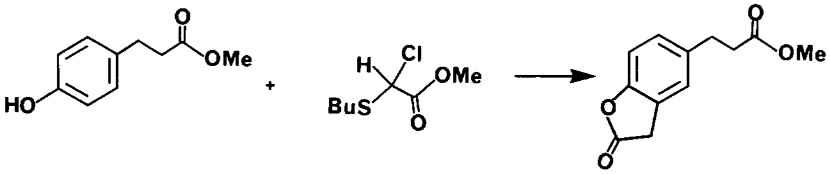
(1)R=H
(5)R=Me

(2)

(3)R=H
(6)R=Me

(4)

the α-(butylthio) substituent was sufficiently activating to permit alkylation of phenols with sulphenylated electrophiles derived from α-chloroacetate also. Thus treatment of phenolic cinnamate (7) with methyl-2-chloro-2-(butylthio)acetate (8) in the presence of zinc chloride, followed by desulphurisation with zinc-acetic acid, furnished lactone (9)^{9}, m.p. 67-68^{0}C, in

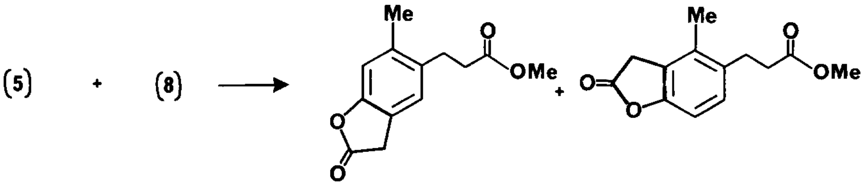


(7)

(8)

(9)

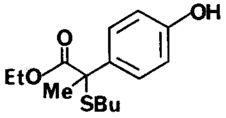
58% overall yield. However, in terms of regioselectivity the sulphenylated α-chloroacetate is less discriminating than the corresponding α-chloropropionate. Thus whereas (5) gave a single alkylated product (6) with chlorosulphide (2), a similar reaction with chlorosulphide (8) gave, after desulphurisation, a 40:60 mixture^{10} of lactones (10) and (11) in 35% yield.



(10)

(11)

This aromatic lactonisation is most successful with phenols in which the para position is blocked. When we applied the procedure to phenol itself and the ethyl ester of chlorosulphide (2), the phenolic ester (12) was the major product (60%)[11] with less than 10% of lactone (13) which was not isolated. p-Cresol and 2-naphthol, on the other hand, underwent smooth lactonisation with chloro-(phenylthio)propionate (14) giving, after reductive desulphurisation, lactone (15)[9] (80%) and (16)[12] (82%), respectively. An attempt was made to extend the process to the synthesis of δ-lactones using benzyl alcohols as substrates. However, p-methylbenzyl alcohol produced less than 15% of a lactone presumed from n.m.r. and i.r. data to be (17), though it was not isolated in a pure state. In summary, this aromatic lactonisation is most successful with p-substituted phenols. Furthermore, the thioether substituent in the product is nicely placed for other functional group manipulations, e.g. production of α-methylene lactones via sulphoxide elimination.



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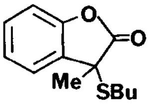

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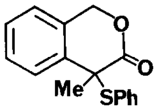

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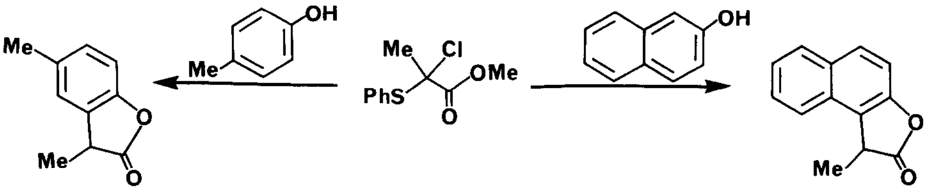

(15) (14) (16)

References and Footnotes

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8. For a recent review of organic synthesis with α-chlorosulphides see B.M. Dilworth and M.A. McKervey, Tetrahedron Reports, in the press.
9. All new compounds gave spectroscopic data consistent with the assigned structures and satisfactory analytical data.
10. The isomer ratio was determined by n.m.r.; the compounds were not separated.
11. This reaction has also been reported by Tamura et al. (ref. 2) who record compound (12) as the sole product. We obtained (12) (60%) with about 30% of a dimeric by-product.
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