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A Novel Route to α-Thiophenyl-γ-Butyrolactones

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A NOVEL ROUTE TO α-THIOPHENYL-γ-BUTYROLACTONES

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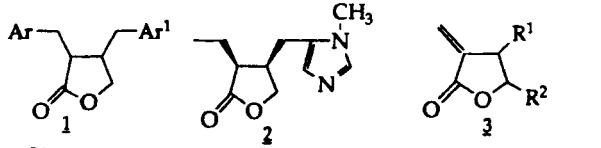
ABSTRACT: An efficient, general route to α-thiophenyl-γ-butyrolactones using an aluminum thiophenoxide mediated Stobbe condensation is described.

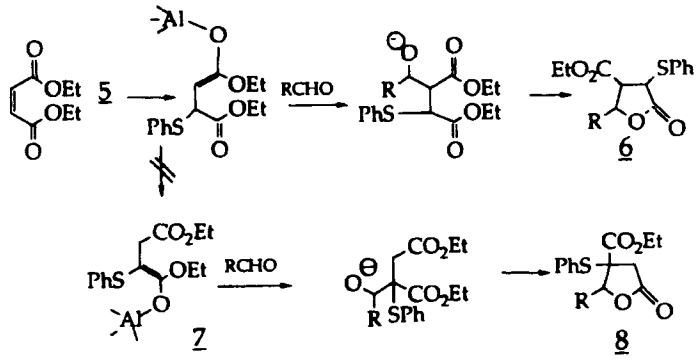
The γ-butyrolactone ring system is ubiquitous in naturally occurring compounds and is therefore a frequent target for organic synthesis. Three examples of biologically active γ-butyrolactone-containing structures are shown below:



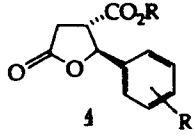
Lignans | Pilocarpine | α-Methylene Lactones

Lignans have been shown to possess anti-tumor activity[1] and to function as growth inhibitors[2a] and anti-fungal agents.[2b] Pilocarpine is a partial muscarinic cholinergic agonist and has been studied recently in relation to Alzheimer's Disease. It is also in clinical use as a topical miotic for controlling intraocular pressure.[3] α-Methylene lactones

Scheme I



have demonstrated activity as anti-tumor agents and antibiotics.[4] Furthermore, the paraconic esters 4 have recently been used as intermediates in the synthesis of thromboxane A_2 antagonists.[5]



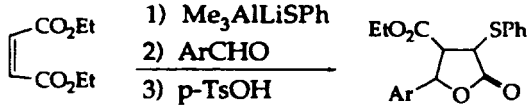
Numerous methods exist for the construction of γ-butyrolactones and, in particular, for paraconic esters.[6] The Stobbe condensation[7] (equation 2) is the most familiar of these methods, although the itaconic half-esters are usually the major products of this reaction.

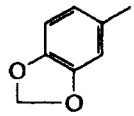
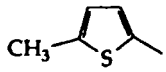
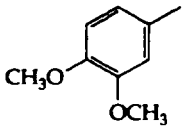
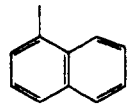
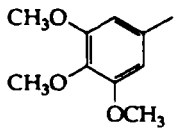
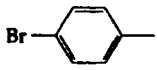
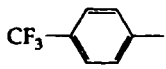
Our interest in the γ-butyrolactone subunit arose from an investigation of the possible synthetic uses of the reagent $(CH_3)_3AlLiSPh$ (5) which had been shown by Oshima to add in a 1,4 manner to α, β-unsaturated esters.[8] We were interested to see whether 5 would react with a 1,2-diactivated olefin, such as diethyl maleate, to

provide an aluminum enolate which would then react with an aldehyde. The resulting hydroxy-ester might next cyclize to give lactone 6 (see Scheme 1).

Two possible problems were anticipated in the development of this methodology. First, it is known that aluminum thiolates can react with esters to provide the corresponding thioesters.[9] Second, it was possible that the initially formed aluminum enolate would undergo a proton transfer to give the more stabilized enolate 7 (Scheme 1). Trapping of this enolate by an aldehyde followed by lactonization would then result in the β-thiophenyl paraconic ester 8. In fact the thiomethyl equivalent of compound 8 has previously been synthesized via a much longer route.[10]

The first examples investigated were those in which an aryl aldehyde was used to trap the aluminum enolate. In each of these reactions, two sets of products were obtained. Thus, the desired lactone was isolated as a mixture of diastereomers and the acyclic hydroxy-ester was isolated, also as a mixture of diastereomers. The ratio of cyclized to uncyclized material was always ~ 1:1 and was independent of reaction time, temperature and the number of equivalents of the aluminum thiolate. Although the lactone and hydroxy-ester were easily separable chromatographically, it was decided that for ease of work-up the crude reaction products would be dissolved in dichloroethane with 0.2 equivalents of p-toluenesulfonic acid and heated to reflux until all of the hydroxy-ester had cyclized. The resulting inseparable mixture of diastereomeric lactones was then isolated and purified. In this manner the following α-thiophenyl-γ-butyrolactones were produced:



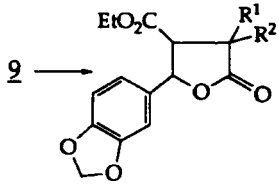
	Ar	Yield [a]
9		85%
10		80
11		83
12		82
13		72
14		51
15		70

a) All compounds were isolated as diastereomeric mixtures.

Unfortunately, this method failed to provide any of the desired product when aliphatic aldehydes were used. In these examples, the only product isolated was the 1,4-addition adduct of thiophenol and diethyl maleate. Also, the reaction did not work for dimethyl maleate, presumably due to competing formation of thioester rather than 1,4-addition. Second, the aluminum ate complex formed from trimethyl aluminum and lithium thiomethoxide did not give any of the desired

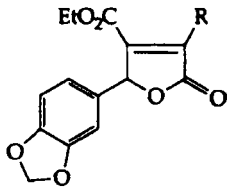
lactone products. Interestingly, the anticipated product (8) from proton transfer (see Scheme 1) was never seen.

The synthetic utility of the α-thiophenyl moiety was demonstrated by its ready interconversion to other functionalities. Thus Raney nickel desulfurization of 9 gave 16. Reaction of 9 with allyltributyltin according to the procedure of Keck[11] gave 17 as a mixture of diastereomers. Also, deprotonation of 9 with LDA followed by alkylation with iodomethane gave the α,α-disubstituted product 18.



16 $R^1 = R^2 = H$ (88%)
17 $R^1 = H$, $R^2 = CH_2CH = CH_2$ (58%)
18 $R^1 = SPh$, $R^2 = CH_3$

Finally, oxidation of the thiophenyl group (m-CPBA, $NaHPO_4$) followed by elimination of the resulting sulfoxide (CCl_4, $CaCO_3$) gave the butenolides 19 and 20 from 9 and 18 respectively.[12] None of the desired exo-methylene compound was seen from the oxidation-elimination of 18.



19 R = H (75%)
20 R = CH_3 (76%)

EXPERIMENTAL SECTION

All reagents and anhydrous solvents were obtained from Aldrich Chemical Company. All reactions were run in oven-dried

glassware under an atmosphere of dry argon. Proton magnetic resonance spectra were measured on a Nicolet QE-300 (300 MHz) instrument. Chemical shifts are reported as δ values (parts per million) relative to Me_4Si as internal standard. Mass spectra were obtained with a Finnegan MAT-90. Infrared spectra were obtained with a Nicolet 20-SXB FT IR. GC/MS Data was obtained with a HP5890A 6C/Finnegan MAT 801 ITD using a 30m x 0.25mm ID, 0.25μm DB-5 column (100°/1 min, 10°/min to 260°).

General Procedure for the Preparation of γ-Butyrolactones

To 50.0 mL of a 0.2M solution (9.80 mmol) of trimethylaluminum-lithium thiophenoxide[8b] in THF, cooled to -78°, was added a solution of 1.534 g (8.91 mmol) of diethyl maleate in 8.0 mL of THF over a 5 min period. The resulting solution was stirred at -78° for 0.5 h and then 13.36 mmol (1.5 equivalents) of the aromatic aldehyde dissolved in 4.0 mL of THF was added dropwise. The reaction mixture was then stirred at -78° for an additional 0.5 h and at 0° for 15 min followed by quenching with 150 mL of saturated NH_4Cl solution.

The reaction was then extracted with ethyl acetate (3 x 150 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then dissolved in 50 mL of dichloroethane, 0.307 g (0.2 equiv.) of p-toluenesulfonic acid was added and the mixture was heated to reflux for 16 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel eluting with ethyl acetate/hexanes (1:3) to provide the α-thiophenyl-γ-butyrolactone as a mixture of diastereomers.

The compounds 9 - 15 were prepared in this manner: (NMR data for the major isomer of the diastereomeric mixture is given).

3-Furancarboxylic acid, 2-(1,3-benzodioxol-5-yl)tetrahydro-5-oxo-4-(phenylthio)-, ethyl ester (9) ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 3.19 (1H, dd, J = 9.2, 10.5 Hz), 4.16 (2H, m), 4.33 (1H, d, J = 10.5 Hz), 5.27 (1H, d, J = 9.2 Hz), 5.95 (2H, s), 6.34 (1H, d, J = 1.8 Hz), 6.52 (1H, dd, J = 1.8, 8.1 Hz), 6.75 (1H, m), 7.39 (3H, m), 7.61 (2H, m); IR (neat) cm^{-1} 2983, 1781, 1734; MS (CI) 404 $(M+NH_4)^+$.

3-Furancarboxylic acid, tetrahydro-2-(5-methyl-2-thienyl)-5-oxo-4-(phenylthio)-, ethyl ester (10) ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.2 Hz), 2.43 (3H, s), 3.36 (1H, dd, J = 9.3, 10.9 Hz), 4.15 (2H, m), 4.33 (1H, d, J = 10.9 Hz), 5. 52 (1H, d, J = 9.3 Hz), 6.57 (1H, m), 6.73 (1H, d, J = 3.5 Hz), 7.39 (3H, m), 7.60 (2H, m); IR (neat) cm^{-1} 1784, 1734; MS (CI) 380 $(M+NH_4)^+$.

3-Furancarboxcylic acid, 2-(3,4-dimethoxyphenyl)tetrahydro-5-oxo-4-(phenylthio)-, ethyl ester (11) ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 3.20 (1H, dd, J = 9.2; 10.9 Hz), 3.76 (3H, s), 3.86 (3H, s), 4.15 (2H, m), 4.35 (1H, d, J = 10.9 Hz), 5.34(1H, d, J = 9.2 Hz), 6.49 (1H, d, J = 2.0 Hz), 6.64 (1H, dd, J = 2.0, 8.1 Hz), 6.76 (1H, d, J = 8.1 Hz), 7.38 (3H, m), 7.62 (2H, m); IR (neat) cm-1 1781, 1734; MS (CI) 420 $(M+NH_4)^+$.

3-Furancarboxylic acid, tetrahydro-2-(1-naphthalenyl)-5-oxo-4-(phenylthio)-, ethyl ester (12) ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 7.2 Hz), 3.88 (1H, dd, J = 3.3, 7.3 Hz), 4.33 (1H, d, J = 3.3 Hz), 6. 13 (1H, d, J = 7.3 Hz), 7.25 - 7.90 (12H, m); IR (neat) cm^{-1} 1785, 1733; MS (CI) 410 $(M + NH_4)^+$.

3-Furancarboxylic acid, tetrahydro-4-(phenylthio)-2-(3,4,5-trimethoxyphenyl)-5-oxo-, ethyl ester (13) ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz), 3.20 (1H, dd, J = 7.1 10.9 Hz), 3.76 (6H, s), 3.82 (3H, s), 4.19

(2H, m), 4.34 (1H, d, J = 10.9 Hz), 5.34 (1H, d, J = 7.1 Hz), 6.26 (2H, s), 7.38 (3H, m), 7.62 (2H, m); IR (KBr) cm^{-1} 1775, 1749; MS (CI) 450 $(M+NH_4)^+$.

3-Furancarboxylic acid, 2-(4-bromophenyl)tetrahydro-5-oxo-4-(phenylthio)-, ethyl ester (14) ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.1Hz), 3.62 (1H, dd, 5.1, 7.9 Hz), 3.67 - 3.83 (2H, m), 4.29 (1H, d, J = 5.1 Hz), 5.51 (1H, d, J = 7.9 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.35 - 7.63 (7H, m); IR (neat) cm^{-1} 1789, 1734; MS (CI) 440 $(M + NH_4)^+$.

3-Furancarboxylic acid, tetrahydro-5-oxo-4-(phenylthio)-2-[3-trifluoromethyl)-phenyl]-, ethyl ester (15) ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 3.62 - 3.80 (3H, m), 4.30 (1H, d, J = 4.5 Hz), 5.59 (1H, d, J = 7.8 Hz), 7.39 - 7.68 (8H, m); IR (neat) cm^{-1} 1779, 1718; MS(CI) 428 $(M + NH_4)^+$.

3-Furancarboxylic acid, 2-(1,3-benzodioxol-5-yl)-5-oxo-4-(2-propenyl)-, ethyl ester (17) (mixture of isomers): ^1H NMR ($CDCl_3$) 1.24 (3H, t, J = 7.2Hz), 2.60 (2H, m), 3.0 - 3.4 (2H, m), 4.20 (2H, m), 5.15 (2H, m), 5.38 (1H, d, J = 9.2 Hz), 5.98 (2H, d J = 2.0 Hz). 5.78 (1H, m), 6.80 (3H, m); IR (neat) cm^{-1} 1781, 1733; MS (CI) 336 $(M+ NH_4)^+$.

3-Furancarboxylic acid, 2-(1,3-benzodioxol-5-yl)tetrahydro-4-methyl-5-oxo-4-(phenylthio)-, ethyl ester (18) ^1H NMR ($CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 1.57 (3H, s), 3.21 (1H, d, J = 9.6 Hz), 4.15-4.35 (2H, m), 5.43 (1H, d, J = 9.8 Hz), 5.90 (2H, dd, J = 1.3, 3.2 Hz), 6.05 (1H, d, J = 1.7 Hz), 6.39 (1H, dd, J = 1.7, 8.0 Hz), 6.61 (1H, d, J = 8.0 Hz), 7.43 - 7.50 (3H, m), 7.66 (2H, m).

3-Furancarboxylic acid, 2-(1,3-benzodioxol-5-yl)2,5-dihydro-5-oxo-, ethyl ester (19) ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz) 4.17 - 4.29 (2H, m), 5.98 (2H, s), 6.06 (1H, d, J = 2.0 Hz), 6.68 (1H, d, J = 1.1 Hz), 6.76 (1H, d, J - 2.2 Hz), 6.80 (2H, d, J = 1.0 Hz); IR (KBr) cm^{-1} 1756, 1726; MS (FAB) 277 (M + H).

3-Furancarboxylic acid, 2-(1,3-benzodioxol-5-yl)-2,5-dihydro-4-methyl-5-oxo-, ethyl ester (20) ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 2.28 (3H , d, J = 2.1 Hz), 4.14-4.27 (2H,m), 5.94 (1H, d, J = 2.1 Hz), 5.98 (2H, s), 6.65 (1H, t, J = 1.0 Hz), 6.78 (2H, d, J = 1.0 Hz); IR (neat) cm^{-1} 1768, 1723; MS (CI) 308 $(M + NH_4)^+$.

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