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INTRAMOLECULAR ACYLATION OF α-SULFINYL CARBANIONS. A SIMPLE PREPARATION OF 4-OXYGENATED SPIRO[4.n]ALK-2-ENE-1-ONES

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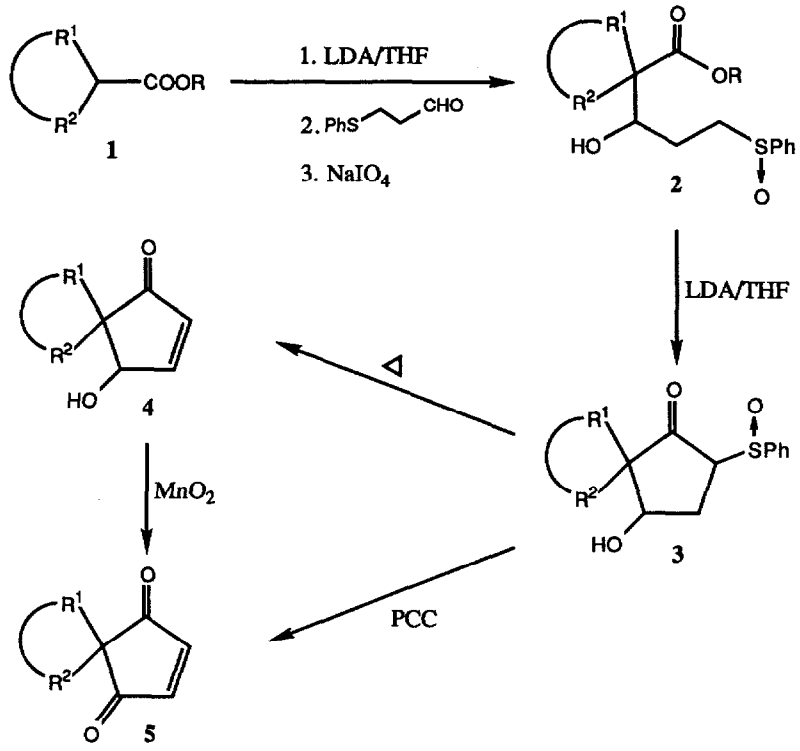
Summary: A convenient synthesis of 4-hydroxy spiro[4.n]alk-2-ene-1-ones and spiro [4.n]alk-2-ene-1,4-diones, which involves the intramolecular acylation of α-sulfinyl carbanions followed by pyrolysis and/or oxidation, is described.

Carbocyclic spiro compounds have attracted considerable attention because of their presence in natural products. Numerous methods for the construction of spirocyclic carbon skeleton have been developed.[1,2] We have recently described the synthetic potential of the intramolecular acylation of α-sulfinyl carbanions for the preparation of 5-substituted, 4,5-disubstituted, 5-alkylidene 2-cyclopentenones[3,4,5] and 6-substituted 2-cyclohexeneones.[6] In conjuction with the above results, we explored the reaction leading to a new efficient method for the annulation of spiro cyclic compounds. As shown in Scheme I, our synthetic sequence started from simple cycloalkane carboxylic esters **1** leading to the 4-oxygenated spiro[4.n]alk-2-ene-1-ones **4** and **5**. The compound of types **4** and **5** should be useful as versatile intermediates for the synthesis of natural products or related compounds.

Thus, treatment of the ester enolate anion derived from the corresponding ester **1** (1 equiv.) and lithium diisopropylamide (LDA, 1.1 equiv) in tetrahydrofuran (THF) with 3-phenylthiopropanal (1.1 equiv) at -78° for 1 hr followed by the oxidation of the resulting hydroxy sulfide with $NaIO_4$ (1.1 equiv) in aqueous methanol at 0° for 10 hr afforded the desired sulfoxide ester **2** in good overall yields. The cyclisation of the sulfoxide ester **2** to the spiro-keto sulfoxide **3** was accomplished by using LDA. Thus, the reaction of the sulfoxide ester **2** (1 equiv) with 3.0-3.3 equivalents of LDA in THF (10 ml/1 mmol of **2**) at -78° for 1 hr and then at 0° for 1-2 hr provided the spiro-keto sulfoxide **3** in good yield as a mixture of diastereomers. The reaction proceeded via the intramolecular acylation reaction of the initially formed α-sulfinyl carbanion derived from the sulfoxide ester **2**.

The spiro-keto sulfoxide **3** could be then converted into the 4-hydroxy-spiro[4.n]alk-2-ene-1-one **4** by pyrolysis at 110-120° under reduced pressure (0.05 Torr). Oxidation of the spiro

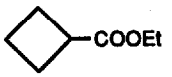
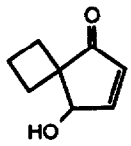
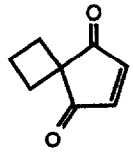
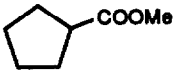
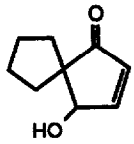
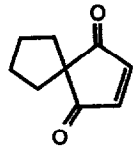
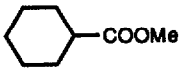
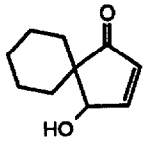
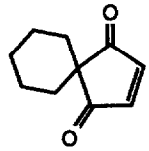
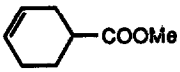
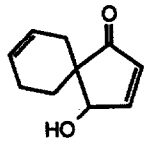
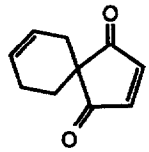
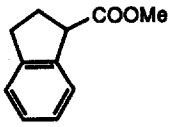
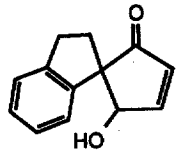
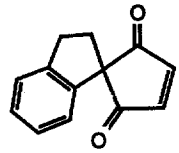
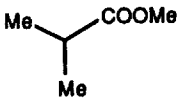
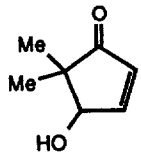
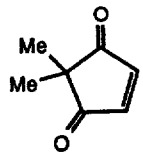
Scheme I



keto sulfoxide **3** with PCC[7] (8 equiv) in CH_2Cl_2 at room temperature for 20 hr gave the spiro[4.n] alk-2-ene-1,4-dione **5**. Attempted oxidation of the keto sulfoxide **3** with other oxidizing agents such as CrO_3/H_2SO_4/acetone and PDC in CH_2Cl_2 or in DMF led to a complex mixture of products as indicated by thin-layer chromatography analysis. The spiro-ene-dione **5** could also be conveniently obtained by the oxidation of the 4-hydroxy-spiro[4.n]alk-2-ene-1-one **4** with excess MnO_2[8] (10 equiv) in CH_2Cl_2 at room temperature for 20 hr. The results are summarized in Table I.

In conclusion, our work has provided a general, convenient route to the oxygen functionalised spiro[4.n]alkene system of types **4** and **5** starting from common cycloalkane carboxylic esters. The spiro compounds of the type **5** have been used as the spiro dienophiles in the synthetic approaches to Fredericamycin A.[10,11] Furthermore, the spiro compounds of the type **4** appear to be valuable intermediates for the synthesis of prostaglandin analogs by three component coupling process[12] which is currently being demonstrated.

Table I Preparation of compounds 2, 3, 4 and 5.

Ester 1	2(%)[a,b,c]	3(%)[a,b,c]	4(%)[a,b]		5[a,b]	3→5(%)	4→5(%)
	61	88		88		65	77
	55	78		51		70	88
	60	90		80		62	82
	65	97		40		72	64
	80	86		78		76	85
	69	92		72		40[d]	not done

a. All products have been characterised by spectral data (IR, ^{1}H-NMR and MS) and elemental analysis for new compounds.

b. Isolated yields after silica gel preparative thin-layer chromatography.

c. Obtained as diastereomeric mixtures.

d. The isolated yield is low due to its volatility.

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