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A general strategy to spiro[4.*n*]alk-2-ene-1,6-diones and spiro[5.*n*]alk-2-ene-1,7-diones via intramolecular acylation of α-sulfinyl carbanions[1]

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Abstract

A convenient and general synthetic method for spiro[4.*n*]alk-2-ene-1,6-diones and spiro[5.*n*]alk-2-ene-1,7-diones, which involves the intramolecular acylation of an α-sulfinyl carbanion, is described.

Keywords: acylation; annulation; carbanions; spiro compounds; sulfoxides.

Spirocarbocyclic systems are of interest because they are commonly found as subunits of many natural products. Synthetic methods directed to these classes of compounds have been extensively developed.[2] In contrast to other procedures that are described for obtaining spirocarbocyclic compounds, there are very few general methods available for the synthesis of spiro[4.*n*]alkane-1,6-diones and spiro[5.*n*]alkane-1,7-diones.[3] In the course of our studies on the intramolecular acylation of sulfinyl carbanions for the preparation of cyclopentenone and cyclohexenone derivatives,[4] we investigated a general route for the construction of spiro[4.*n*]alk-2-ene-1,6-diones and spiro[5.*n*]alk-2-ene-1,7-diones. These compounds are highly functionalized intermediates, which may be useful for further synthetic conversions.

Starting from readily available cyclic β-ketoesters **1a**–**c**, the sulfoxides **2** or **3** could be obtained in good overall yields by a simple base-catalyzed alkylation using 1,3-dibromopropane or 1,4-dibromobutane (NaH/DMF, room temperature, overnight) followed by treatment of the resulting bromides with a tetrahydrofuran solution of thiophenol and triethylamine, at 0°C to room temperature overnight, and then oxidation of the resulting sulfides with sodium metaperiodate in aqueous methanol at 0°C. Having considered the structures of the sulfoxides **2** and **3**, it was found that the difference in acidities of the protons alpha to the carbonyl and to the sulfinyl groups should allow selective deprotonation by an appropriate base. As shown in Scheme 1, effective cyclization of the sulfoxides **2** and **3** to the desired spiro-diones **7** and **8** required the protection of the carbonyl group in order to avoid the competitive

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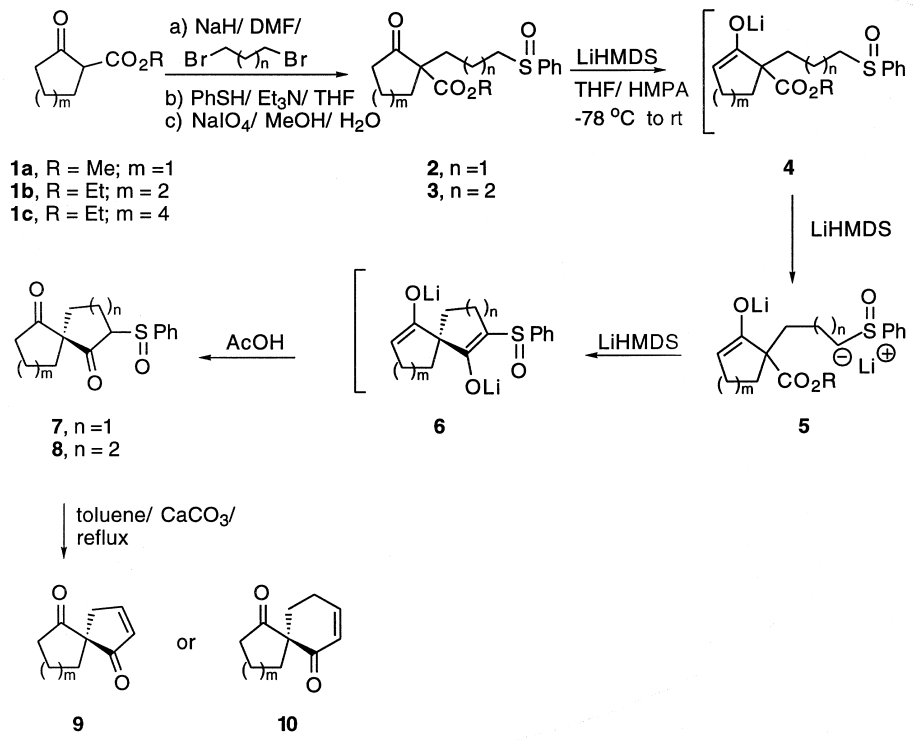
proton abstraction. We therefore planned to protect the carbonyl group as its enolate anion **4** before the α-sulfinyl carbanion **5** was generated. Intramolecular acylation of α-sulfinyl carbanion **5** was expected to provide the dienolate **6** and then the spiro-diones **7** and **8** after acidic workup. Initially, cyclisation of the sulfoxide **2a** was attempted by employing lithium diisopropylamide (LDA) as a base.



Scheme 1.

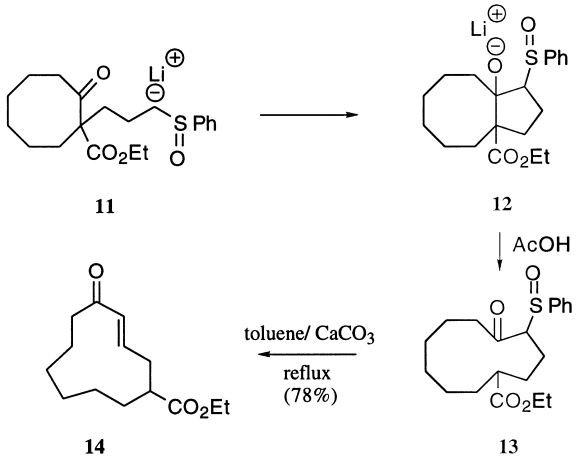
Thus, treatment of the sulfoxide **2a** with LDA (4.0 equiv.) in tetrahydrofuran at −78°C for 1 h and at 0°C for 2 h afforded a complex mixture of unidentified products. The reaction in the presence of hexamethylphosphoramide (HMPA) under the same conditions gave similar results. These unsatisfactory results might be due to low selectivity for the deprotonation of protons alpha to the keto and sulfinyl groups of the sulfoxide **2a** by the LDA and incomplete formation of the enolate anion **4** before formation of the α-sulfinyl carbanion **5**. On the other hand, treatment of the sulfoxide **3a** under the same reaction conditions afforded the expected spiro-dione **8a** in 46% yield as a diastereomeric mixture after radial chromatography. Cyclisation of the sulfoxide **3b** under these conditions provided, however, a low yield (20% yield) of the spiro-dione **8b** along with a complex mixture of products. These unsatisfactory results led us to use a less reactive base such as lithium hexamethyldisilazide (LiHMDS). As expected, when the sulfoxide **2a** was subjected to reaction with 4–4.5 equivalents of LiHMDS in THF in the presence of HMPA at −78°C to room temperature overnight, followed by quenching the reaction mixture with glacial acetic acid, the spiro-dione **7a** was isolated in 83% yield as a diastereomeric mixture. Cyclization of the other sulfoxides of types **2** and **3** was investigated and found to proceed smoothly to give the corresponding spiro[4.*n*]dione **7** and spiro[5.*n*]dione **8** in moderate to good yields. The results are summarized in Table 1. It is worthy to note that under the standard conditions, the 8-membered ketosulfoxide **2c** provided the desired spiro-dione **7c** in 40–45% yield along with the ring-expansion product **13** in 45% yield (Table 1, entry 3). Compound **13** resulted presumably from the intramolecular

Table 1
Preparation of the starting sulfoxides **2** and **3**, spiro-diones **7** and **8** and spiro-endiones **9** and **10**

Entry	Ketoesters	Sulfoxides (%)[a,b,c,d]	Spiro-diones (%)[a,b,c,d]	Spiro-endiones (%)[a,b,e]
1	**1a**, m = 1	**2a**, n = 1 (86%)	**7a**, n = 1 (83%)	**9a** (59%)
2	**1b**, m = 2	**2b**, n = 1 (87%)	**7b**, n = 1 (87%)	**9a** (65%)
3	**1c**, m = 4	**2c**, n = 1 (93%)	**7c**, n = 1 (40-45%)	**9c** (75%)
4	**1a**, m = 1	**3a**, n = 2 (86%)	**8a**, n = 2 (58%)	**10a** (80%, 68%[f])
5	**1b**, m = 2	**3b**, n = 2 (86%)	**8b**, n = 2 (73%)	**10b** (83%, 66%[f])
6	**1c**, m = 4	**3c**, n = 2 (87%)	**8c**, n = 2 (80%)	**10c** (83%, 56%[f])

[a] All products were fully characterized by spectral data (IR; ^{1}H- and ^{13}C- NMR; MS) and elemental analyses.
[b] Isolated yields: % yields of the sulfoxides **2** and **3** were calculated based on the ketoesters **1**.
[c] Obtained as diastereomeric mixtures.
[d] Purified by radial chromatography (SiO_2).
[e] Purified by preparative thin-layer chromatography (SiO_2).
[f] Cyclization of the sulfoxides **2** and **3** followed by pyrolysis of the resulting crude spiro-diones **7** and **8** was carried out.

nucleophilic addition of the initially formed α-sulfinyl carbanion **11** to the carbonyl group of the cyclooctanone moiety followed by ring-expansion of the resulting β-alkoxyester **12** (Scheme 2).

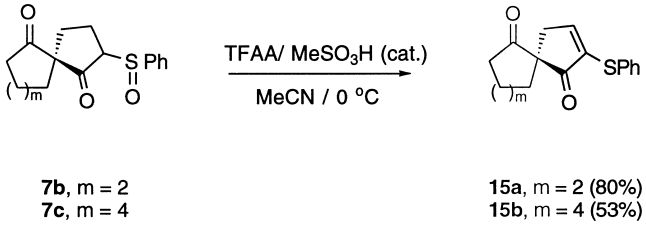


Scheme 2.

Finally, conversion of the spiro-diones **7** and **8** into the corresponding spiro[4.*n*]alk-2-ene-1,6-diones **9** and spiro[5.*n*]alk-2-ene-1,7-diones **10** could be accomplished in good yields by refluxing in dry toluene in the presence of calcium carbonate for 10 h as summarized in Table 1. Similarly, compound **13** could be converted into compound **14** in 78% yield as the (*E*)-isomer under the same conditions.

To demonstrate the synthetic utility of our spiroannulation reaction, the spiro-ketosulfoxides **7b** and **7c** were transformed into phenylthio-substituted spiro-dienones **15a** and **15b** in moderate yields by performing the Pummerer rearrangement using trifluoroacetic anhydride in acetonitrile in the presence of a catalytic amount of methanesulfonic acid (0°C, 2 h) (Scheme 3).[5] This type of highly functionalized spiro compound may be useful in organic synthesis.

In summary, we have developed a general and facile approach for the construction of spiro[4.*n*]alk-2-ene-1,6-diones **9** and spiro[5.*n*]alk-2-ene-1,7-diones **10** starting from simple cyclic β-ketoesters. These types of spiro compound appear to be valuable intermediates in organic synthesis.



7b, m = 2
7c, m = 4

15a, m = 2 (80%)
15b, m = 4 (53%)

Scheme 3.

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