

# Intramolecular carbonyl olefination of esters. Regioselective preparation of enol ethers of cyclic ketones by the titanocene(II)-promoted reaction of alkyl $\omega,\omega$ -bis(phenylthio)alkanoates

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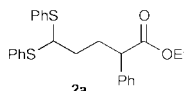
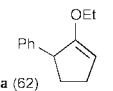
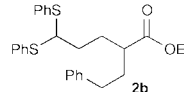
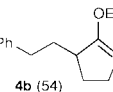
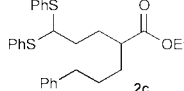
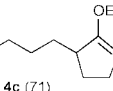
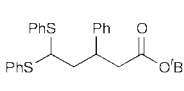
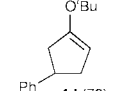
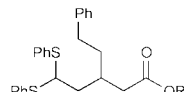
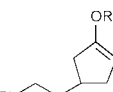
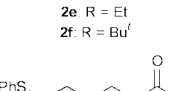
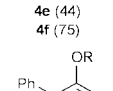
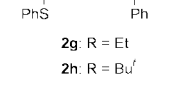
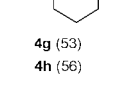
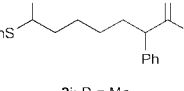
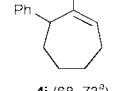
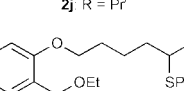
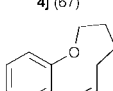
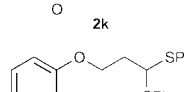
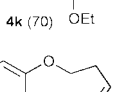
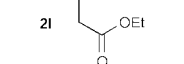

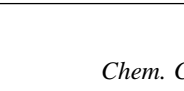
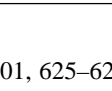
The treatment of alkyl  $\omega,\omega$ -bis(phenylthio)alkanoates with  $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$  produced enol ethers of 5-, 6-, 7-, and 9-membered cyclic ketones.

Intramolecular reactions of phosphorous ylides and related  $\alpha$ -phosphorous carbanions with ketones and aldehydes have been used by a number of workers for the preparation of cycloalkenes, including complex natural products.<sup>1</sup> However, intramolecular carbonyl olefinations of esters using the phosphorous carbanions are generally unsuccessful because these reactions end up with the formation of acylation products.<sup>2</sup> Only the preparation of certain five- and six-membered cyclic compounds, in which the formation of a double bond is facilitated by  $\pi$ -conjugation with a carbonyl group or an aromatic ring, has been achieved.<sup>3</sup> Transition metal-carbene complexes and related reagents have been employed for this transformation. Stille and Grubbs have described the formation of titanium-carbene complexes by the ring-opening metathesis of strained norbornylene derivatives and their intramolecular reaction with an ester carbonyl.<sup>4</sup> Although tungsten-carbene complex promoted transformation of benzyl 2-benzylhex-5-enoate into 3-benzyl-2-benzylloxycyclopentene *via* olefin metathesis-carbonyl olefination was reported, the experimental details including the yield of the product were not disclosed.<sup>5</sup> Mortimore and Kociński reported the cyclization of 4,4-dibromobutyl benzoate utilizing a  $\text{TiCl}_4$ -Zn-TMEDA system.<sup>6</sup> The olefination product, 6-phenyl-3,4-dihydro-2H-pyran, however, was obtained in only a poor yield. The intramolecular McMurry coupling of keto esters is regarded as a formal intramolecular olefination of esters, and various cyclanones have been prepared by this method.<sup>7</sup> Although this reaction is useful for the preparation of furans and benzofurans,<sup>8</sup> its application to the synthesis of alicyclic vinyl ethers has yet to appear. Formal intramolecular carbonyl olefination consisting of the intermolecular carbonyl olefination of esters and subsequent ring closing metathesis has been employed for the synthesis of cyclic vinyl ethers.<sup>9</sup> The studies described above indicate that the intramolecular carbonyl olefination of esters still remains a problem to be solved.

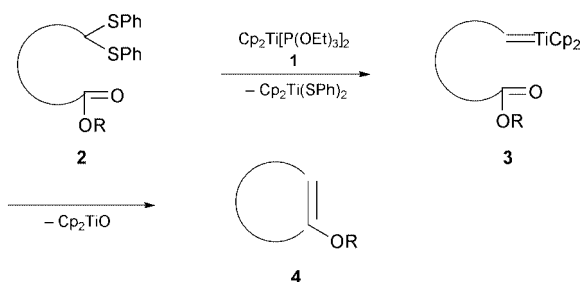
Recently we reported a new method for carbonyl olefination using a thioacetal- $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$  1 system.<sup>10</sup> Since this reaction is useful for the olefination of esters, we have studied

its application to the synthesis of cyclic vinyl ethers. Unfortunately the attempt to prepare monocyclic vinyl ethers by

**Table 1** Intramolecular carbonyl olefination of alkyl  $\omega,\omega$ -bis(phenylthio)alkanoates 2

Entry	Ester 2	Temp. (Time/h)	Product 4 (Yield/%)
1		reflux (2)	 <b>4a</b> (62)
2		15 °C (3)	 <b>4b</b> (54)
3		rt (3)	 <b>4c</b> (71)
4		rt (5)	 <b>4d</b> (70)
5		reflux (2)	 <b>4e</b> (44)
6		rt (3)	 <b>4f</b> (75)
7		reflux (3)	 <b>4g</b> (53)
8		reflux (3)	 <b>4h</b> (56)
9		reflux (3)	 <b>4i</b> (68, 73 <sup>a</sup> )
10		reflux (3)	 <b>4j</b> (67)
11		rt (3)	 <b>4k</b> (70)
12		rt (5)	 <b>4l</b> (67)

<sup>a</sup> The reaction was performed on a 5 mmol scale.



**Scheme 1**

the titanocene(II)-promoted olefination of  $\omega,\omega$ -bis(phenylthio)alkyl alkanoates was unsuccessful owing to the concomitant formation of oligomers.<sup>11</sup> Herein we describe the intramolecular reaction of alkyl  $\omega,\omega$ -bis(phenylthio)alkanoates **2**. This reaction proceeds by way of the titanium–carbene complexes **3** to produce a wide variety of vinyl ethers of cyclic ketones **4** without formation of any oligomer (Scheme 1).

When methyl 2-phenyl-7,7-bis(phenylthio)heptanoate **2i** was treated with the low-valent titanium species **1** (4 equiv.) at room temperature for 1 h, the complete disappearance of the starting material was observed. Column chromatography using basic alumina gave the cyclic vinyl ether **4i** in 59% yield. The cyclization of **2i** in refluxing THF produced **4i** in better yield (Table 1, Entry 9). In a similar manner, the enol ethers of five-, six-, and seven-membered cyclic ketones were obtained in good yields by the reaction of alkyl  $\alpha$ -substituted  $\omega,\omega$ -bis(phenylthio)alkanoates. The substituent  $\alpha$  to the carbonyl group is not crucial for the present olefination. The reactions of the esters carrying a substituent at the  $\beta$ -position also produced the corresponding cyclic compounds **4d–f**.<sup>†</sup> It was found that the *tert*-butyl esters gave better yields than the corresponding ethyl esters in these reactions (see Entries 5 and 6). In some case, we observed the partial isomerization of the initial olefination product to the tetrasubstituted cycloalkene. This isomerization, however, was absolutely depressed when the reaction was carried out at 15 °C (Entry 2).

The advantage of the present preparation is that the starting materials are easily prepared by the use of organosulfur building blocks. Thus the esters **2k** and **1** were obtained by the Williamson ether synthesis utilizing  $\omega,\omega$ -bis(phenylthio)alkanoles and were transformed into the nine-membered cyclic vinyl ethers **4k** and **1** with high stereoselectivity. The *E*-configuration of their double bonds was determined by NOESY.

All the experiments described above were carried out on a small scale (0.5 mmol). Since an intramolecular reaction generally requires high dilution conditions to prevent the competitive intermolecular reaction, decrease in the yield is sometimes a serious problem upon scale up. We examined a gram-scale reaction of **2i** to confirm the synthetic utility of the present reaction. Using a slightly modified procedure,<sup>12</sup> the cycloheptene **4i** was obtained in better yield (73%) than for the smaller scale reaction (Entry 9).

In conclusion, we have established the first versatile method for the regioselective preparation of vinyl ethers of cyclic ketones by the intramolecular carbonyl olefination of esters. Further study on the application of this methodology to the synthesis of a variety of heterocycles is currently in progress.

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## Notes and references

<sup>†</sup> A typical experimental procedure: to 6 ml of a THF solution of the titanocene(II) reagent **1**, prepared from titanocene dichloride (498 mg, 2.0 mmol), magnesium turnings (58 mg, 2.4 mmol), triethyl phosphite (0.69 ml, 4.0 mmol), and finely powdered molecular sieves 4 Å (200 mg),<sup>13</sup> was added 10 ml of a THF solution of **2f** (237 mg, 0.50 mmol) dropwise over 20 min at room temperature under argon. After stirring for 3 h, the reaction was quenched by addition of 1 M NaOH (20 ml). The insoluble materials were filtered off through Celite and washed with ether (10 ml). The layers were separated, and the aqueous layer was extracted with ether (3 × 30 ml). The combined organic extracts were washed with 1 M NaOH (20 ml) and dried over K<sub>2</sub>CO<sub>3</sub>. After removal of the solvent, the residue was chromatographed over alumina gel (deactivated with 5% of H<sub>2</sub>O; eluted with 1% triethylamine in hexane) to afford 92 mg (75%) of **4f**.

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