

Carbonyl Olefination by Means of a *gem*-Dichloride–Cp₂Ti[P(OEt)₃]₂ System

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The preparation of highly substituted olefins by carbonyl olefination using a *gem*-dichloride–Cp₂Ti[P(OEt)₃]₂ system was studied. The treatment of organotitanium species, formed by reaction with titanocene(II) species from *gem*-dichlorides having two alkyl substituents, with an aldehyde or ketone afforded tri- or tetrasubstituted olefins in good yields. Acyclic or cyclic trisubstituted vinyl ethers were also obtained by a similar reaction using carboxylic esters or lactones as carbonyl components.

Introduction

The olefination of carbonyl compounds is one of the most fundamental transformations in organic synthesis, and a variety of methods have been investigated. Among them, the Wittig,¹ Honer–Wadsworth–Emmons,² and Peterson³ reactions have been widely used for this transformation. Despite the usefulness of these reactions, several problems persist. One of the objections to their application to organic synthesis is the fact that they are not capable of being employed for the olefination of carboxylic acid derivatives. However, this limitation has been overcome by the use of titanium-based reagents. The titanium methylidene formed from Tebbe reagent, Grubbs' titanacyclobutanes, and Petasis' dimethyltitanocene is useful for the Wittig-like methylenation of carboxylic acid derivatives.⁴ As for the alkylidenation, a 1,1-dihaloalkane–Zn–TiCl₄ system has been investigated by Takai, Utimoto, and their co-workers,⁵ and Petasis et al. reported the olefination of carboxylic acid derivatives using certain diorganotitanocenes.⁶ Recently, we also reported a carbonyl olefination using the organotitanium compound formed from the titanocene(II) species Cp₂Ti[P(OEt)₃]₂ (**1**) and thioacetal, which effects the alkylidenation of carboxylic esters, lactones, and thioesters.⁷

Another major problem of carbonyl olefination is its application to the preparation of highly substituted olefins. It is well known that the olefination of carbonyl compounds is largely affected by steric hindrance, and the yields are generally very low in the case of tetrasub-

stituted olefins.⁸ The reactions of phosphoryl-stabilized carbanions and α -silyl carbanions proceed smoothly when only one alkyl group is present at the central carbon of these carbanions. Therefore, the preparation and reaction of these species possessing two α -alkyl substituents have been the subjects of little synthetic work. Only isopropylidene⁹ and cycloalkylidene-phosphoranes¹⁰ and similar α -phosphoryl¹¹ and α -silyl-carbanions,¹² whose substituents present minimal steric hindrance to the approaching carbonyl compound, are prepared and employed for carbonyl olefination. Although Aguero et al. reported the olefination of carbonyls using tungsten-alkylidene complexes, only the cyclopentylidene complex was employed for the preparation of tetrasubstituted olefins.¹³ The synthesis of a tetrasubstituted olefin using a titanium-based reagent has not yet appeared, which may be due to difficulties in the preparation of the titanium reagent required for such a transformation.

Unfortunately, our thioacetal–Cp₂Ti[P(OEt)₃]₂ procedure suffered a similar disadvantage; the olefination using thioacetal formed from dialkyl ketone was unsuccessful due to the slow reaction of thioacetal with **1** and the preferential formation of alkenyl sulfide during the preparation of the active species.¹⁴ We then turned our attention to the synthesis of highly substituted olefins using *gem*-dihalides. Since the carbon–halogen bond

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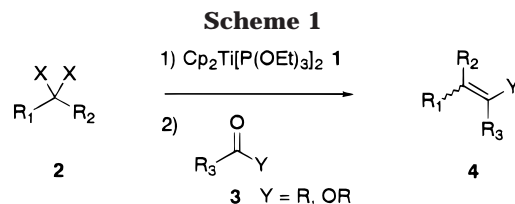
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would be more easily reduced with titanocene(II) **1** than the carbon-sulfur bond of thioacetal, the organotitanium species, such as the alkylidenetitanocene having an α -substituent or its equivalent, would be formed by the treatment with **1** of a *gem*-dihalide having two alkyl substituents (**2**). The resulting active species would then afford the tri- or tetrasubstituted olefin on treatment with an aldehyde or ketone (Scheme 1). The synthetic application of *gem*-dihalides **2** has so far been largely restricted because their selective preparation is generally difficult owing to the concomitant formation of vinyl halides and the vigorous reaction conditions required when carbonyl compounds are employed as starting materials. However, now these compounds are regarded as readily available materials since we have recently found an operationally straightforward and inexpensive method for the preparation of *gem*-dihalides **2** which consists of the transformation of ketones to the hydrazones and their treatment with copper(II) halide-triethylamine in methanol.¹⁵

Results and Discussion

The reaction of heptanal **3a** with the titanium reagent formed by the treatment of 3,3-dibromo-1-phenylbutane **2a** (2 equiv) with the titanocene(II) complex **1** (6 equiv) produced the trisubstituted olefin **4a** in only 34% yield (Table 1, entry 1). However, **4a** was obtained in acceptable yield when the corresponding dichloride **2b** was employed (entry 2). As would be expected, the olefination of dialkyl ketone **3b** and cyclic ketone **3c** with **2b** also proceeded to afford the tetrasubstituted olefins (entries 3 and 4). Under similar reaction conditions, olefinations of ketones and aldehydes with several dichlorides **2** were performed. The results summarized in Table 1 indicate that tetrasubstituted olefins with three or less acyclic alkyl substituents are prepared in good yields by the present procedure. On the other hand, the preparation of an olefin having four alkyl substituents is still a problem to be solved. For example, it was found that the olefination of 3-pentanone **3b** with the *gem*-dichloride **2c** was messy, and the corresponding tetrasubstituted olefin was obtained in less than 17% yield.

The alkylation of carboxylic esters provides a great advantage over other methods for enol ether synthesis because no ambiguity exists as to the location of the double bond in the product. Although this is especially the case for trisubstituted vinyl ethers, conventional olefination procedures are ineffective for the preparation

Table 1. Olefination of Carbonyl Compounds

Entry	<i>gem</i> -Dihalide	Carbonyl Compound	Product (Ratio of Stereoisomers) ^a	Yield(%) ^b
1			 (40 : 60) ^c	34
2			 (40 : 60) ^c	57
3				59
4				79
5			 (60 : 40)	83
6			 (90 : 10)	74
7 ^d			 (75 : 25)	62
8				64
9				58
10 ^e				69
11				72
12				50
13				52
14				73
15				81

^a Determined by ¹H NMR spectroscopy. ^b Isolated yield based on the carbonyl compound used. ^c *E:Z*. The stereochemistry was assigned by comparison with the authentic *E*-isomer. ^d The carbonyl compound was treated with the organotitanium species for 15 h. ^e The reaction was carried out at 0 °C.

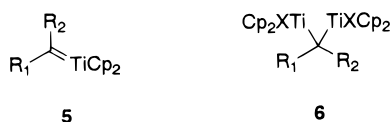
of such compounds. When we examined the olefination of carboxylic esters using *gem*-dichlorides, we found that vinyl ethers were obtained in good yields even when the product possessed three acyclic alkyl substituents (entries

(14) The olefination of 4-*tert*-butylcyclohexanone using 2,2-bis(phenylthio)propane gave 1-isopropylidene-4-*tert*-butylcyclohexane in 63% yield,^{7a} whereas the yield of olefination of the same ketone was largely decreased (31%) when 2,2-bis(phenylthio)butane was employed. The treatment of 1,5-diphenyl-3,3-bis(phenylthio)pentane with 3 equiv of **1** at room temperature for 2 h afforded 1,5-diphenyl-5-(phenylthio)-pent-2-ene (44%) and the partial reduction product 1,5-diphenyl-3-phenylthiopentane (33%).

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5, 6, 12, and 15). Lactones were also transformed into trisubstituted cyclic vinyl ethers (entries 7 and 11).

On the basis of the fact that the titanium species formed from thioacetal and titanocene(II) **1** shows the reactivities characteristic of transition-metal carbene complexes,¹⁶ we suppose that the olefination using thioacetal–titanocene(II) proceeds via the alkylidenetitanocene **5**. It is also reasonable to assume that the active intermediate of this reaction would be the same as that of olefination using thioacetal. However, a pathway that involves the reaction of geminal dimetallic species **6** with a carbonyl compound is not neglected at this stage.



In summary, we have developed a new carbonyl olefination system for the preparation of highly substituted olefins which utilizes easily accessible *gem*-dichlorides and titanocene(II) species. This procedure is the first practical method for the transformation of carboxylic esters and lactones to trisubstituted enol ethers.

Experimental Section

General. ¹H (500 MHz) and ¹³C (125 MHz) NMR spectra were recorded with CDCl₃ as the solvent. All reactions were performed under an argon atmosphere in dried glassware. For thin-layer chromatography, Wakogel B-5F was used as an adsorbent. THF was distilled from sodium and benzophenone. Since water prevents the reduction of Cp₂TiCl₂, the dried reagents should be used for the preparation of titanocene(II) species **1**.

Reaction of 3,3-Dichloro-1-phenylbutane (2b) with Heptanal (3a). To a flask charged with finely powdered 4A molecular sieves (150 mg), magnesium turnings (73 mg, 3 mmol), and Cp₂TiCl₂ (747 mg, 3 mmol) were added successively

(16) The titanium species prepared by the reaction of thioacetal with **1** reacts with alkene,^{16a} alkyne,^{16b} allylsilane,^{16c} and trialkylsilane and related group 14 organometallics^{16d} to produce cyclopropane, conjugated diene, γ -substituted allylsilane, and [2+1]carbenoid insertion products, respectively: (a) Horikawa, Y.; Nomura, T.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Org. Chem.* **1997**, *62*, 3678. (b) Takeda, T.; Shimokawa, H.; Miyachi, Y.; Fujiwara, T. *Chem. Commun.* **1997**, 1055. (c) Fujiwara, T.; Takamori, M.; Takeda, T. *Chem. Commun.* **1998**, 51. (d) Takeda, T.; Nozaki, N.; Fujiwara, T. *Tetrahedron Lett.* **1998**, *39*, 3533.

THF (4 mL) and P(OEt)₃ (1.06 mL, 6 mmol) with stirring at room temperature. Within 15 min, the reaction mixture turned dark green and then dark brown with a slight evolution of heat. After 3 h, **2b** (203 mg, 1 mmol) in THF (1 mL) was added to the reaction mixture, which was further stirred for 20 min. Next, **3a** (57 mg, 0.5 mmol) in THF (2 mL) was added. After being stirred for 1 h, the reaction mixture was diluted with hexane (30 mL) and the insoluble materials were filtered off through Celite. The filtrate was condensed under reduced pressure. The crude product was purified by PTLC (hexane:AcOEt = 95:5) to yield 65 mg (57%) of 3-methyl-1-phenyldec-3-ene (**4a**, *E:Z* = 40:60): ¹H NMR δ 0.84–0.92 (m, 3H), 1.17–1.34 (m, 8H), 1.64 (s, 1.2H), 1.72 (s, 1.8H), 1.82–1.92 (m, 1.2H), 1.92–2.00 (m, 0.8H), 2.24–2.36 (m, 2H), 2.62–2.73 (m, 2H), 5.09–5.19 (m, 1H), 7.09–7.30 (m, 5H); ¹³C NMR δ 14.11, 16.07, 22.67, 23.44, 27.80, 27.92, 28.97, 29.09, 29.77, 29.94, 31.83, 34.01, 34.49, 34.77, 41.66, 125.38, 125.59, 125.70, 126.27, 128.17, 128.22, 128.36, 134.10, 134.16, 142.43, 142.48; IR (neat) 2958, 2929, 2856, 1604, 1496, 1454, 1377, 742, 698 cm⁻¹. Anal. Calcd for C₁₇H₂₆: C, 88.63; H, 11.37. Found: C, 88.86; H, 11.61.

Reaction of 2b with Methyl Phenylacetate (3d). To a THF (3 mL) solution of **1** prepared from finely powdered 4A molecular sieves (200 mg), magnesium turnings (44 mg, 1.8 mmol), Cp₂TiCl₂ (448 mg, 1.8 mmol), and P(OEt)₃ (0.62 mL, 3.6 mmol) was added **2b** (126 mg, 0.6 mmol) in THF (0.5 mL), and the reaction mixture was stirred for 20 min. Next, **3d** (45 mg, 0.3 mmol) in THF (1 mL) was added dropwise over 8 min, and the mixture was further stirred for 1 h. The usual workup gave 2-methoxy-3-methyl-1,5-diphenylpent-2-ene (**4d**, 66 mg, 83%, ratio of stereoisomers = 60:40): ¹H NMR δ 1.70 (s, 1.2H), 1.77 (s, 1.8H), 2.31–2.37 (m, 1.2H), 2.45–2.52 (m, 0.8H), 2.62–2.75 (m, 2H), 3.28 (s, 1.2H), 3.37 (s, 1.8H), 3.39 (s, 1.2H), 3.53 (s, 0.8H), 7.08–7.32 (m, 10H); ¹³C NMR δ 14.90, 16.76, 32.80, 32.99, 33.03, 34.38, 34.70, 35.33, 56.69, 56.77, 118.11, 118.23, 125.61, 125.80, 125.93, 125.97, 128.11, 128.14, 128.27, 128.33, 128.35, 128.45, 128.51, 139.06, 139.10, 141.97, 142.48, 148.30, 149.01; IR (neat) 3024, 2962, 2931, 1643, 1452, 1240, 1194, 698 cm⁻¹. Anal. Calcd for C₁₉H₂₂O: C, 85.67; H, 8.32. Found: C, 85.81; H, 8.42.

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Supporting Information Available: Characterization data for compounds **4b**, **4c**, and **4e–m** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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