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Preparation of enol ethers by carbonyl olefination utilizing an alkoxymethyl chloride–titanocene(II) system

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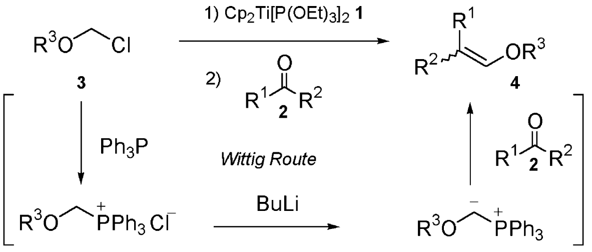
Abstract—Aldehydes, ketones, esters and lactones are transformed into enol ethers or 1,2-dialkoxy-1-alkenes by treatment with organotitanium species prepared from alkoxymethyl chlorides and a titanocene(II) complex.

Enol ethers are useful intermediates in organic synthesis and a variety of methods for their preparation have been investigated. Among them alkoxymethylenation of carbonyl compounds by the Wittig reaction using alkoxymethylenephosphoranes has been most frequently employed as a useful method for the one carbon homologation of carbonyl compounds to aldehydes.[1] The similar methoxymethylenation by the Peterson reaction utilizing methoxy(trimethylsilyl)methyllithium was also reported.[2] A serious drawback of these conventional reactions is that they cannot be employed for the olefination of carboxylic acid derivatives due to the preferential acylation. On the other hand, methoxymethylenation utilizing titanium-based reagents eliminates such limitation; a variety of carbonyl compounds are transformed into enol ethers by the treatment with methoxymethylidene–titanocene(II) species **1**.[3] However, inaccessibility of various dithioorthoformates has prevented the use of this procedure as a versatile method for alkoxymethylenation.

Recently, we found a new carbonyl olefination utilizing an alkyl halide–titanocene(II) system.[4] We further investigated the application of this new methodology to the synthesis of various olefins, and here we report a versatile method for the alkoxymethylenation of carbonyl compounds **2** utilizing alkoxymethyl chlorides **3** and titanocene(II) **1** leading to the formation of enol ethers or 1,2-dialkoxy-1-alkenes **4**. It largely simplifies the conventional Wittig route as shown in Scheme 1. The present reaction enjoys the advantage that the halides **3** are used as olefination agents without any pre-transformation, and the starting materials **3** were readily prepared from the corresponding alcohols by the reaction with paraformaldehyde and hydrogen chloride.[5]

Treatment of benzyloxymethyl chloride **3a** with the titanocene(II) species **1** at −20°C for 5 min and 25°C for 10 min produced certain organotitanium species, which afforded the enol ether **4a** in 66% yield on treatment with 1,5-diphenyl-3-pentanone **2a** (Table 1, Entry 1). When the reaction of the organotitanium species with **2a** was carried out under reflux in THF, the yield of the enol ether **4a** slightly increased (Entry 2). Similar reactions of aldehydes and ketones **2b**–**e** with various alkoxymethyl chlorides **3** were performed and the enol ethers **4b**–**h** were obtained in good yields (Entries 3–9).[6]

The following is a typical experimental procedure. Finely powdered molecular sieves 4 A (175 mg), magne-



Scheme 1. Titanocene(II)-promoted alkoxymethylenation of carbonyl compounds with alkoxymethyl chlorides.

Keywords: carbonyl compounds; enol ethers; olefination; titanium and compounds.

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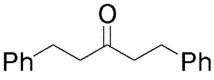
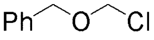
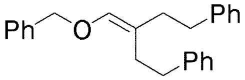
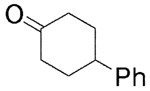
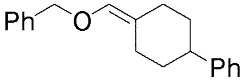
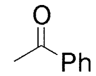
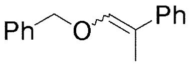
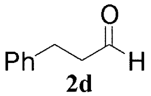
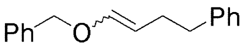
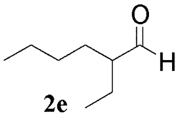
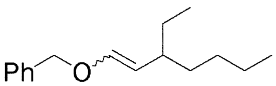
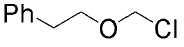
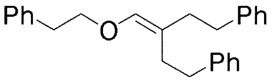
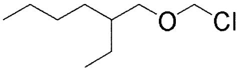
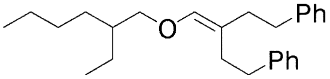
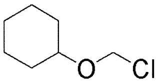
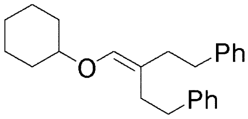
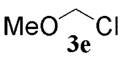
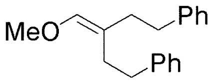
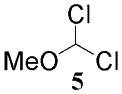
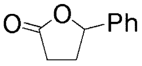
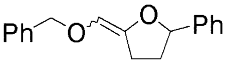
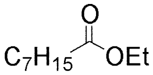
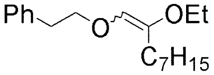
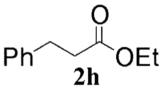
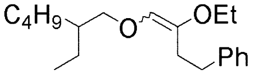
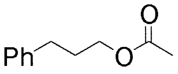
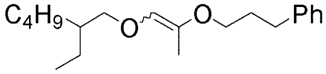
Table 1. Alkoxymethylenation of carbonyl compounds[a]

Entry	Carbonyl compound **2**	Alkoxymethyl chloride **3**	Product **4** (Yield / %; E : Z[b])	
1[c]	 **2a**	 **3a**		**4a** (66)
2	**2a**	**3a**		**4a** (70)
3	 **2b**	**3a**		**4b** (60)
4	 **2c**	**3a**		**4c** (67; 73 : 27)
5	 **2d**	**3a**		**4d** (49; 74 : 26)
6	 **2e**	**3a**		**4e** (58; 87 : 13)
7	**2a**	 **3b**		**4f** (70)
8	**2a**	 **3c**		**4g** (63)
9	**2a**	 **3d**		**4h** (62)
10	**2a**	 **3e**		**4i** (52)
11	**2a**	 **5**		**4i** (66)
12[d]	 **2f**	**3a**		**4j** (82; 69 : 31[e])
13	 **2g**	**3b**		**4k** (76; 62 : 38)
14	 **2h**	**3c**		**4l** (85[f]; 60 : 40)
15	 **2i**	**3c**		**4m** (81; 61 : 39[e])

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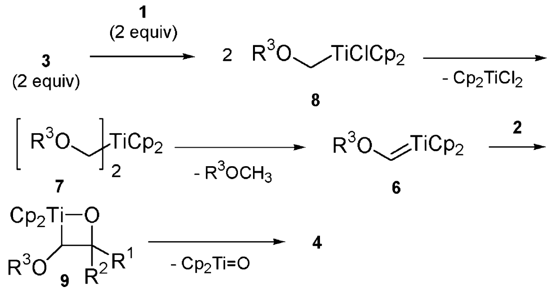
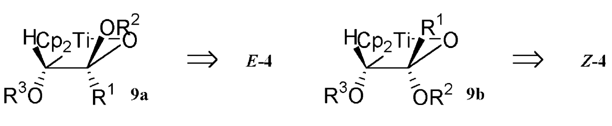
[a] All the reactions were performed with a similar procedure as described in the text, unless otherwise noted. [b] Determined by NMR analysis. [c] Carried out at 25 °C for 3 h. [d] The reaction was quenched after addition of Et_3N (1 mL/1 mmol of **2f**). [e] Based on the isolated yields. [f] Contaminated with 2-ethylhexyl methyl ether. The yield was corrected for the contaminant.

sium turnings (43 mg, 1.8 mmol) and Cp_2TiCl_2 (436 mg, 1.75 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (3.5 ml) and $P(OEt)_3$ (0.60 mL, 3.5 mmol) were added successively with stirring at room temperature under argon, and the reaction mixture was stirred for 2.8 h. The mixture was cooled to −20°C and a THF (1 mL) solution of **3a** (235 mg, 1.5 mmol) was added. After being stirred for 5 min, the mixture was warmed up to 25°C and stirring was continued for further 10 min at the same temperature. A THF (1.5 mL) solution of **2a** (119 mg, 0.50 mmol) was added to the mixture. After refluxing for 3 h, the reaction was quenched by addition of 1 M NaOH. The insoluble materials were filtered off through Celite and washed with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over K_2CO_3. After removal of the solvent, the residue was purified by silica gel PTLC (hexane/ethyl acetate = 95/5, v/v) to afford 105 mg (70%) of **4a**. **CAUTION** Alkoxymethyl chlorides are powerful alkylating agents and potential carcinogens.

As shown in Entry 10, the reaction of methoxymethyl chloride **3e** with **2a** resulted in the formation of the enol ether **4i** in unsatisfactory yield probably due to hydrogen chloride formed by the partial hydrolysis of the halide during weighting. Based on our previous observation that a *gem*-dihalide–titanocene(II) **1** system olefinated the carbonyl compounds through the formation of an alkylidene titanocene as an intermediate,[7] we explored the use of dichloromethyl methyl ether **5** for the methoxymethylenation of **2a** and found that the enol ether **4i** was obtained in better yield (Entry 11).[8] It is of interest that the both reactions using the monochloride and the dichloride afford the same enol ether.[9] Since the dihalide **5** is commercially available, this reaction is a good alternative for the methoxymethylenation with **3e**.



Scheme 2. Plausible pathway for the formation of enol ethers.



Scheme 3. Oxatitanacyclobutane intermediates in the alkoxymethylenation of esters and lactones.

The present alkoxymethyl chloride–titanocene(II) **1** system can be applied to esters and lactones **2f–i**. Using a similar procedure,[10] these carbonyl compounds were transformed into the 1,2-dialkoxy-1-alkenes **4j–m** in good yields (Entries 12–15).

As illustrated in Scheme 2, we assume that the reaction proceeds through the formation of the alkoxymethylidene complex of titanium **6**. The complex **6** is generated by α-elimination of dialkyltitanocene **7**, produced by the oxidative addition of the chloride **3** to titanocene(II) species, and subsequent disproportionation of the resulting alkyltitanocene **8**.[11] Similarly to other titanium carbene complexes, the titanocene–alkoxymethylidene **6** reacts with a carbonyl compound **2** to afford the corresponding olefin **4** via the formation of oxatitanacyclobutane intermediate **9**.

In the present alkoxymethylidenation of esters and lactones, the *E* isomers always predominated.[12] The observed selectivity is different from that of the alkylidenation of carboxylic acid derivatives with titanocene-alkylidenes, in which *Z*-isomers are always dominant products.[13] This is probably due to the unfavorable formation of the oxatitanacyclobutane intermediate **9b**, which is destabilized by the dipole–dipole repulsion between two alkoxy substituents (Scheme 3).

In summary, we have established the first general method for the alkoxymethylenation of carbonyl compounds using alkoxymethyl chlorides and titanocene(II) species, which is operationally straightforward and needs no strong base such as alkyllithium. Further study on the synthetic application of an alkyl halide–titanocene(II) system is currently under way.

Acknowledgements

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6. The present alkoxymethylenation of the aromatic aldehydes such as benzaldehyde and 1-naphthaldehyde resulted in the formation of complex mixtures and the olefination products were obtained in poor yields.
7. Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem*. **1998**, *63*, 7286.
8. The reaction was carried out by the procedure similar to that employed for the reaction using alkoxymethyl chloride **3**. Dichloromethyl methyl ether **5** (0.14 mL, 1.5 mmol) was added at −40°C to a THF (4 mL) solution of titanocene(II) reagent **1**, prepared from Cp_2TiCl_2 (3.0 mmol), magnesium turnings (3.0 mmol) and $P(OEt)_3$ (6.0 mmol), and the mixture was stirred for 20 min. The mixture was warmed up to −10°C and a THF (1 mL) solution of **2a** (119 mg, 0.50 mmol) was added over 10 min. After stirring for 3 h, the reaction was quenched by addition of 1 M NaOH. The usual work-up and purification gave 88 mg of **4i** in 66% yield.
9. The methoxymethylenations of methyl 1-naphthyl ketone with the monochloride **3e** and the dichloride **5** gave 1-(1-methyl-2-methoxyethenyl)naphthalene in 44 and 54% yields, respectively. Almost identical stereoselectivity (*E*:*Z* = 70: 30 for **3e**, 72: 28 for **5**) suggested that both reactions proceed through the formation of the same active intermediate.
10. The reaction was performed with the same procedure as described for aldehydes and ketones using the following molar ratio of the reagents: Cp_2TiCl_2:Mg:$P(OEt)_3$: **2**:**3** = 4.5:4.5:9:1:4. The products could be isolated by silica gel PTLC without any precaution.
11. In the alkoxymethylenation of **2a** with **3a**, the formation of phenethyl methyl ether in an amount corresponding to the olefination product **4f** was observed, supporting the reaction path depicted in Scheme 2.
12. Configuration of the trisubstituted olefins **4c**,**j–m** was determined by NOE experiment.
13. (a) Petasis, N. A.; Bzowej, E. I. *J. Org. Chem*. **1992**, *57*, 1327; (b) Petasis, N. A.; Akritopoulou, I. *Synlett* **1992**, 665; (c) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc*. **1997**, *119*, 1127; (d) Takeda, T.; Watanabe, M.; Nozaki, N.; Fujiwara, T. *Chem. Lett*. **1998**, 115; (e) Hart, S. L.; McCamley, A.; Taylor, P. C. *Synlett* **1999**, 90.