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Carbonyl olefination utilizing an alkyl halide–titanocene(II) system

Takeshi Takeda,* Keiko Shimane, Kenji Ito, Naoko Saeki and Akira Tsubouchi
Department of Applied Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan. E-mail: takeda-t@cc.tuat.ac.jp; Fax: +81 42 388 7034; Tel: +81 42 388 7034

Received (in Cambridge, UK) 21st June 2002, Accepted 26th July 2002
First published as an Advance Article on the web 7th August 2002

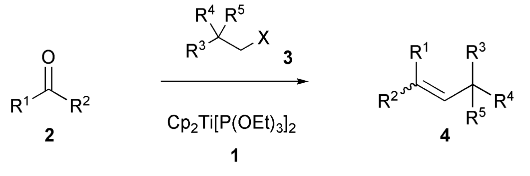
Ketones, aldehydes, esters and lactones are transformed into olefins by treatment with the organotitanium species formed from alkyl halides and titanocene(II).

Olefination of carbonyl compounds is one of the most fundamental transformations in organic synthesis and a variety of procedures have been investigated. For the one-pot conversion of carbonyl compounds to olefins, the Wittig,[1] Horner–Wadsworth–Emmons[2] and Peterson[3] reactions, and the Kocieński–Julia olefination[4] are frequently employed. The Tebbe and related titanium-based reagents[5] and *gem*-dizinc compounds[6] are also useful for the direct transformation of carboxylic acid derivatives to heteroatom-substituted olefins.

We disclosed an alternative method for the Wittig-like olefination of carbonyl compounds utilizing a thioacetal–titanocene(II) $Cp_2Ti[P(OEt)_3]_2$ **1** system.[7] In connection with this study, we investigated the reactions of organic dihalides with titanocene(II) reagent **1**[8] and recently reported the preparation of cyclopropanes by the reductive cyclization of 1,3-dihalides with **1**,[9] the first step of which is undoubtedly the oxidative addition of the halide to **1** to form alkyltitanocene species. We further investigated the reactivity of organotitanium species produced by the reaction of simple alkyl halides with **1** and observed that such species generated from alkyl halides bearing a β-substituent behave like titanium carbene complexes. In this communication, we describe an extremely straightforward procedure for the olefination of carbonyl compounds **2** utilizing alkyl halides **3** and titanocene(II) reagent **1** (Scheme 1).†

Although the successive treatment of *n*-butyl iodide **3a** with titanocene(II) species **1** and 1,5-diphenyl-3-pentanone **2a** afforded no olefination product, the similar treatment of alkyl halides **3** possessing a substituent at the carbon β to halogen produced the olefins **4**. Table 1 summarizes the results of the reactions of various alkyl halides **3** with **2a**. It is apparent that the yield of carbonyl olefination is largely dependent on bulkiness of the substituent. The yield of **4** increased with increase in the carbon number of the alkyl groups attached to the β-carbon and was maximized when the halides **3** have an ethyl group as a β-substituent. The olefination proceeded using the corresponding alkyl bromides or chlorides, though a slight decrease in the yields of olefins **4** was observed. Successful olefination was also attained by the use of neopentyl iodide which has no β-hydrogen.[10]

More than two equivalents of alkyl halide were required to complete the reaction in every case, and the dehalogenated hydrocarbon was produced in *ca.* 50% yield (based on the halide used) by the olefination utilizing the alkyl iodide **3f**. Therefore it is rational to assume that the reaction follows the sequence illustrated in Scheme 2. Disproportionation of the alkyltitanium species **5** produced by the oxidative addition of alkyl halide **3** to the titanocene(II) species **1** affords the dialkyltitanocene **6**. Its α-elimination of the respective alkane gives the titanium carbene complex **7**, which reacts with a carbonyl compound to produce the olefin **4** *via* the oxatitanacyclobutane **8**.



Scheme 1

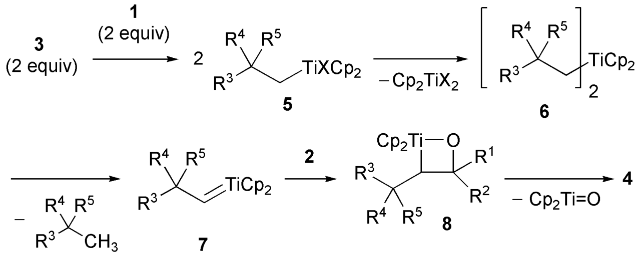
It is unclear at present why a β-substituent is essential for the formation of the carbene complex. One plausible explanation is that it interferes β-elimination of **6**. If β-elimination of **6** proceeds *via* the four-membered cyclic transition state **9** as depicted in Scheme 3, the steric non-bonding interaction between the ligand coordinated to the titanium atom and the bulky β-substituent destabilizes the transition state **9** and prevents the β-elimination. Consequently the decomposition through α-elimination preferentially proceeds to afford the carbene complex **7**.

Using several alkyl iodides possessing a β-substituent, olefinations of ketones and aldehydes were performed, and the

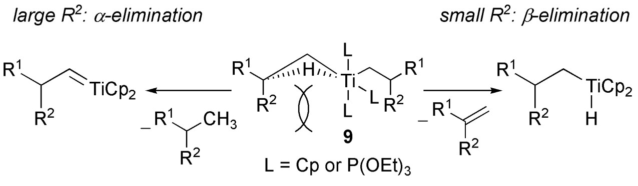
Table 1 Olefination of 1,5-diphenyl-3-pentanone **2a** with various alkyl halides **3**[a]

3	R^3	R^4	R^5	X	Product yield (%)	
3a	Et	H	H	I	**4a**	—
3b	Me	Me	H	I	**4b**	11
3c	Et	Me	H	I	**4c**	42
3d	Et	Et	H	I	**4d**	64
3e[b]	Bu	Et	H	I	**4e**	60
3e[c]	Bu	Et	H	I	**4e**	66
3f	$PhCH_2$	$PhCH_2$	H	I	**4f**	60
3g	$PhCH_2$	$PhCH_2$	H	Br	**4f**	57
3h	$PhCH_2$	$PhCH_2$	H	Cl	**4f**	56
3i	Me	Me	Me	I	**4g**	56

[a] All reactions were carried out with the method described in the text, unless otherwise noted. [b] The ketone **2a** was treated with the organotitanium species for 2 h. [c] Three equiv. of **3e** were used.



Scheme 2



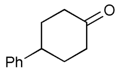
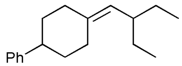
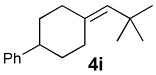
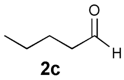
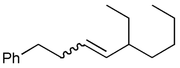
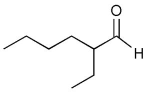
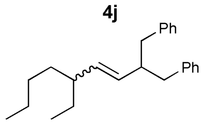
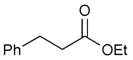
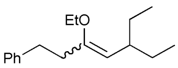
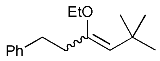
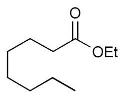
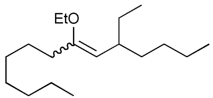
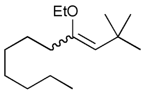
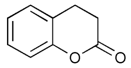
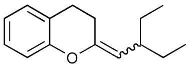
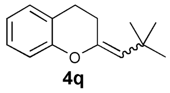
Scheme 3

DOI: 10.1039/b205983e

corresponding olefins **4** were obtained. The present olefination is also applicable to carboxylic acid derivatives, and vinyl ethers were produced in good yields (Table 2).

α-Elimination of transition metal alkyl complexes is a versatile tool for the preparation of metal carbenes. This process, however, suffers a serious drawback in that a carbene complex generally cannot be formed from an alkyl complex possessing alkyl groups with β-hydrogen due to preferential β-elimination.[11] The preparation of titanium carbene complexes by the α-elimination of dialkyltitanocenes and their application to carbonyl olefination have been investigated by Petasis *et al.*[12] They prepared dialkyltitanocenes from titanocene dichloride and organolithiums or Grignard reagents. Because dialkyltitanocenes capable of a facile β-elimination are thermally unstable,[13] a limited number of organotitanium species such as dimethyl-,[14] dibenzyl-,[15] bis(trimethylsilylmethyl)-,[16] bis(cyclopropyl)-,[17] and bis(alkenyl)-titanocenes[18] are employed for this procedure.

Table 2 Carbonyl olefination utilizing an alkyl iodide–titanocene(II) system[a]

Carbonyl compound **2**	Alkyl iodide	Product	Yield (%) (*E*:*Z*)[c]
 **2b**	**3d**[b]	 **4h**	65
2b	**3i**[b]	 **4i**	58
 **2c**	**3e**[b]	 **4j**	59 (51 : 49)
 **2d**	**3h**	 **4k**	62 (68 : 32)
 **2e**	**3d**	 **4l**	77 (24 : 76)
2e	**3i**	 **4m**	62 (13 : 87)
 **2f**	**3e**	 **4n**	79 (24 : 76)
2f	**3i**	 **4o**	64 (12 : 88)
 **2g**	**3d**	 **4p**	86 (29 : 71)
2g	**3i**	 **4q**	64 (34 : 66)

[a] All reactions were carried out with the method described in the text, unless otherwise noted. The carbonyl compounds **2e–g** were treated with the organotitanium species at 25 °C for 5 min and then under reflux for 2 h. [b] Three equiv. of **3** were used. [c] The configurations of **4l–q** were determined by NOE experiments.

The most striking feature of the present reaction is that the Wittig-like olefination of carbonyl compounds including carboxylic acid derivatives is accomplished by the use of readily available alkyl halides without any pre-transformation. At the same time, our finding demonstrates that the titanium carbene complexes are produced by α-elimination of dialkyltitanocene even when the alkyl substituent has a β-hydrogen.

This research was supported by a Grant-in-Aid for Scientific Research (No. 14340228) and a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' (No. 14044022) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

† *A typical experimental procedure*: finely powdered molecular sieves 4 A (175 mg), magnesium turnings (43 mg, 1.75 mmol; purchased from Nacalai Tesque Inc. Kyoto, Japan) 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 reaction mixture was cooled to −20 °C and stirred for 15 min. A THF (1 ml) solution of **3d** (286 mg, 1.35 mmol) was added to the mixture and stirring was continued for 5 min at the same temperature. After being warmed up to 25 °C, the mixture was further stirred for 10 min. A THF (1.5 ml) solution of **2a** (119 mg, 0.5 mmol) was added to the reaction mixture. After the mixture had been stirred for 3 h, the reaction was quenched by addition of 1 M NaOH (30 ml). The insoluble materials were filtered off through Celite and washed with diethyl ether (40 ml). The layers were separated, and the aqueous layer was extracted with ether (2 × 20 ml). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by PTLC [hexane–ethyl acetate (98 : 2, v/v)] to yield 98 mg (64%) of **4d**.

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