THE METHYLENATION OF ENOLIZABLE KETONES AND ESTERS USING ORGANOTITANIUM CHEMISTRY

Leigh Clawson, Stephen L. Buchwald[1] and Robert H. Grubbs*

Contribution No. 6973 from the Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

Abstract: The titanium methylidene fragment, $Cp_2Ti=CH_2$, resulting from Tebbe's reagent, $Cp_2TiCH_2 \cdot AlMe_2Cl$ or the β,β-disubstituted metallacycle, $Cp_2TiCH_2C(Me)(n\text{-}Pr)CH_2$, methylenates enolizable acidic ketones and converts α,α-disubstituted ketones into titanium enolates. The reagent reacts selectively with ketones over esters.

The Wittig reaction, using methylene triphenylphosphorane, remains the most generally useful procedure for the conversion of ketones and aldehydes to terminal olefins.[2] Since its development, many alternate methods have been introduced to expand the utility of this reaction. Most important have been Corey's development of the dimsyl anion in DMSO[3] and the α-lithiomethylene triphenylene phosphorane[4] as a means to coax hindered or unreactive ketones to undergo methylenation.
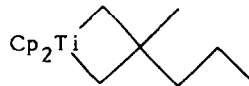
The standard Wittig reagents can function as strong bases, removing the acidic α-proton of carbonyl compounds. With easily enolizable ketones, proton abstraction becomes the dominant reaction. We report here results which show that the titanocene methylene fragment 1 will cleanly convert enolizable ketones to olefins
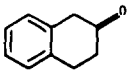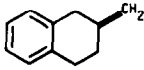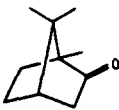
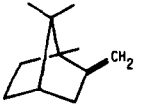$$Cp_2Ti=CH_2 \qquad Cp_2Ti \underset{Cl}{\overset{}{\diagup\!\!\diagup}} AlMe_2 \qquad Cp_2Ti \diagup\!\!\diagdown\!\!\diagup\!\!\diagdown$$
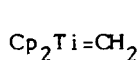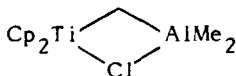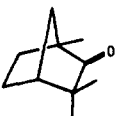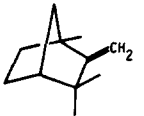
$$\text{1} \qquad\qquad\qquad \text{2} \qquad\qquad\qquad\qquad \text{3}$$

rapidly at or below room temperature. In addition, as previously reported for 2,[5] 1 derived from either 2 or 3 will cleanly convert esters and lactones into their corresponding enol ethers. Moreover, while 1 is extremely reactive, it shows a high preference for reaction with ketones over esters. For example, in competition

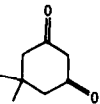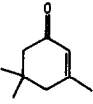experiments in which an equimolar solution of acetophenone and methyl benzoate, β-methyl styrene and β-methoxy styrene are produced in the ratio of 25-30:1.

In Table I are listed examples of methylenations and isolated yields of a variety of enolizable ketones using both 2 and 3. Even notoriously enolizable ketones such as β-tetralone, give a high yield of the terminal olefin. Moreover, cyclic ketones which often give only low yields of products under standard Wittig conditions[3] at room temperature or below are essentially quantitatively converted to their corresponding olefins. In particular, 2-phenylcylopentanone gives only a 55% yield of the carbonyl addition product on treatment with methyl lithium.[6] In comparison, a >90% yield of olefins is isolated using either 2 or 3. Only in the case of the extremely hindered ℓ-fenchone is a low yield observed. In a related example, the reaction of the β-diketone dimedone with two equivalents of 2 followed by an acidic workup gives a high yield of isophorone. Presumably, the first equivalent of 2 reacts with dimedone to form the metalate. A second equivalent then adds to the vinylogous acid carbonyl.
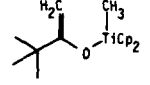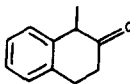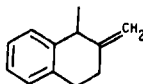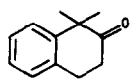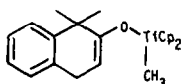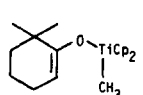
Table I

Substrate	Product	3	2	Substrate	Product	3	2
		~70[a]	84[a]			~70[b]	87
		100	93			20	0
		98	89			--	70[c]

[a] Stirred at room temperature 8 h to allow for decomposition of relatively stable metallacycle to olefin product. [b] NMR Yield. [c] Two equivalents of 2 used with acidic workup.

The choice of 2 or 3 as the source of the titanium methylene, 1, is largely dictated by experimental convenience, or the need for high selectivity, since the yields are comparable for the two reagents. For example, 2 is commercially available and can be used in the temperature range -40°C to room temperature. It is compatible with ethereal solvents at low temperatures and with aromatic hydrocarbons or methylene chloride at all temperatures (non-ethereal solvents require the use of at least one equivalent of pyridine). The major disadvantage is that dimethylaluminum chloride or the aqueous workup may cause unwanted side reactions and other complications. Compound 3 can be prepared from 2 using a modification of our standard procedure.[7] It reacts rapidly at ⁓6°C or above and is compatible with ethereal or aromatic solvents. Reactions with ketones generally require less than 2 min. Moreover, the reactions are easier to workup. Typical experimental procedures are given below.

Table 2

| Substrate	Product[a]	Substrate	Product
(structure)	(structure)	(structure)	(structure)
(structure)	(structure)	(structure)	(structure)
(structure)	(structure)	(structure)	(structure)

[a]Yields of 85-90% for enolates and >95% for olefins determined by NMR by integration of products relative to isobutylene.

Reaction with **2**: A solution of **2** (313 mg, 1.1 mmol) in 4 mL THF (pre-cooled to -40°C) is prepared under Ar. To this is added 1.0 mmol of ketone or ester. After stirring at -40°C for 30 min, the reaction mixture is allowed to warm to room temperature over 90 min. The reaction is quenched by the dropwise addition of 0.3 m L of 15% aqueous NaOH to the cooled (-10 to -15°C) reaction mixture. After warming to room temperature, the resulting dark green solution is diluted with ∼50 mL of Et_2O, dried ($MgSO_4$), filtered through celite, and concentrated. The crude product is further purified by filtration through a short column of silica gel or alumina (neutral, activity III).

Reaction with **3**: A solution of **3** (304 mg, 1.1 mol) in 4 mL of Et_2O (pre-cooled to 0°C) is prepared under Ar. To this is added 1.0 mmol of ketone or ester. The reaction mixture is allowed to warm to room temperature over ∼30 min and then diluted with ∼50 mL of pentane and filtered through celite. Further purification is effected as described for the reaction with **2**.

Upon further investigation of the reaction of **1** with carbonyl compounds, it was discovered that **1** reacts quite differently with most α,α-disubstituted ketones. These compounds react with **1** to afford titanium enolates instead of the expected olefin. If one compares the ketones in Tables 1 and 2, it can be seen that the enolization (path b) is due to the steric crowding that blocks the methylene transfer pathway through an oxymetallacycle (path b) rather than the acidity of an α-hydrogen or the displacement of a good leaving group as in anhydrides[8] and acid chlorides.[9]

The enolates in the reaction of **1** with ketones are less reactive than those produced with acid chlorides and anhydrides. They are quite thermally stable and do not undergo aldol condensations with aldehydes. This is thought to be a consequence of decreased Lewis acidity of the titanium center due to the attached methyl group.
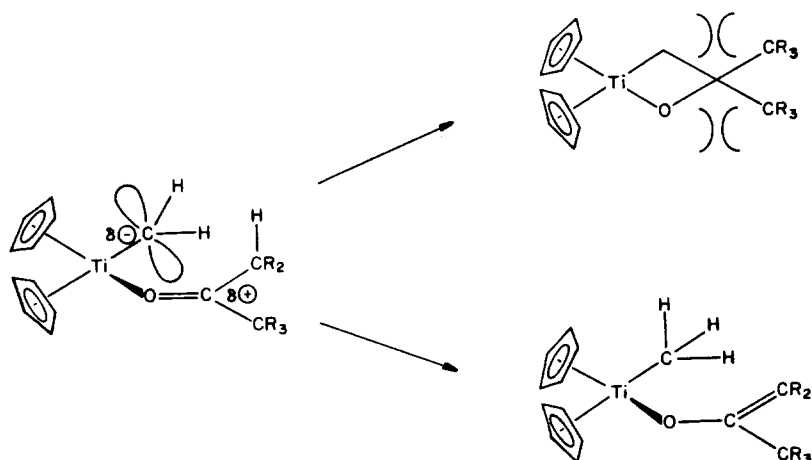
In conclusion, we have shown that titanocene methylene 1, formed from either 2 or 3, cleanly converts even the most easily enolizable ketones, excepting those which are α,α-disubstituted to their corresponding olefin compounds.

References and Notes

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