



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

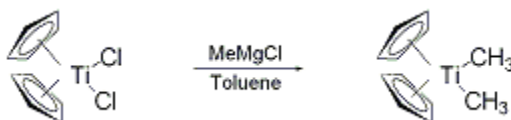
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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DIMETHYLTITANOCENE

[Titanium, *bis*(η^5 -2,4-cyclopentadien-1-yl)dimethyl-]



Submitted by Joseph F. Payack¹, David L. Hughes¹, Dongwei Cai¹, Ian F. Cottrell², and Thomas R. Verhoeven.¹

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1. Procedure³

A 1-L, three-necked, round-bottomed flask, equipped for mechanical stirring, and outfitted with a 250-mL, pressure equalizing addition funnel, and a Claisen adapter bearing a thermometer and a nitrogen inlet/outlet vented through a mineral oil bubbler, is placed under a nitrogen atmosphere and charged with 41.5 g (0.167 mol) of titanocene dichloride (Note 1), and 450 mL of dry toluene (Note 2). The slurry is efficiently stirred and chilled to an internal temperature of -5°C in a ice/methanol bath; then 126 mL of a 3 M solution (0.38 mol) of methylmagnesium chloride in tetrahydrofuran (THF) (Note 1) is added dropwise via the addition funnel over 1 hr, at a rate of addition adjusted to maintain an internal temperature below $+8^{\circ}\text{C}$. The resulting orange slurry (Note 3) is mechanically stirred at an internal temperature of 0 to $+5^{\circ}\text{C}$ for 1 hr, or until the insoluble purple titanocene dichloride is no longer seen in the suspension (Note 4). The addition funnel is removed and replaced by a rubber septum, and the reaction is assayed by ^1H NMR (Notes 5, 6).

While the reaction is aging at 0° to $+5^{\circ}\text{C}$, a 2-L, three-necked, round-bottomed flask, equipped for mechanical stirring, and outfitted with a rubber septum, and a Claisen adapter bearing a thermometer and a nitrogen inlet/outlet vented through a mineral oil bubbler, is placed under a nitrogen atmosphere and charged with 117 mL of 6% aqueous ammonium chloride (7.0 g diluted to 117 mL) (Note 1). The solution is chilled to 1 to 2°C , with efficient mechanical stirring. When the formation of dimethyltitanocene is judged to be complete, the toluene/THF reaction mixture is quenched into (Note 7) the well-stirred aqueous ammonium chloride solution via a cannula (Note 8) over a period of 1 hr, maintaining an internal temperature of 0° to $+5^{\circ}\text{C}$ in both flasks. Toluene (30 mL) is used to rinse the reaction flask. The biphasic mixture is then poured into a 2-L separatory funnel, with another 30 mL of toluene rinse, and the aqueous phase is separated (Note 9). The organic layer is washed sequentially with three portions of cold water (100 mL each) and brine (100 mL), then dried over anhydrous sodium sulfate (Na_2SO_4 , 35 g). The organic layer is filtered and carefully (Note 10) concentrated under reduced pressure on a rotary evaporator at a bath temperature of no more than 35°C to a weight of 150 g. The resulting orange solution is assayed by ^1H NMR (Note 11) to be 20 weight percent dimethyltitanocene (29.55 g, 85.0%). If the solution is to be stored for more than a week, the reagent should be diluted with 160 mL of dry THF (Note 2), which has a stabilizing effect on the labile reagent (Note 12). The solution is stored at 0° to 10°C under nitrogen in a rubber septum-sealed, round-bottomed flask. It proved effective in the conversion of a complex ester to an enol ether (Note 13).

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc., and used without further purification.
2. This solvent was purchased from Fisher Scientific Company and dried over 3\AA sieves to a water content of less than 150 $\mu\text{g/mL}$ by Karl Fisher titration.
3. The sparingly soluble titanocene dichloride reacts in stepwise fashion with methylmagnesium chloride to give the soluble red $\text{Cp}_2\text{Ti}(\text{Me})\text{Cl}$, then the soluble orange dimethyltitanocene, precipitating magnesium chloride (MgCl_2). The mixture becomes thick with MgCl_2 , as the reaction proceeds and

vigorous stirring is required.

4. Since the **titanocene dichloride** is insoluble and the intermediate $\text{Cp}_2\text{Ti}(\text{Me})\text{Cl}$ is soluble, the second methyl group adds much faster than the first. Reaction progress can be monitored by visually observing the disappearance of the purple crystalline **titanocene dichloride**.

5. A ca. 200 μL -sample is removed via *wide* bore syringe or pipet (so that a representative sample is pulled from the heterogeneous reaction mixture) and is quenched into 1 mL of water. The mixture is extracted with 1 mL CDCl_3 , the organic phase is dried with **sodium sulfate**, and the solution is filtered into an NMR tube. The progress is evaluated by observing the Cp singlets: the reaction is considered complete when less than 3% combined of **titanocene dichloride** and $\text{Cp}_2\text{Ti}(\text{Me})\text{Cl}$ remains by ^1H -NMR.

6. The spectra are as follows: ^1H NMR (CDCl_3) Cp_2TiMe_2 : δ 6.05 (s, 10 H), -0.05 (s, 6 H). Cp_2TiClMe : δ 6.22 (s, 10 H), 0.80 (s, 3 H). Cp_2TiCl_2 : δ 6.56 (s, 10 H). ^{13}C NMR Cp_2TiMe_2 : δ 113.20 (Cp_2), 45.77 (Me_2). Cp_2TiClMe : δ 115.86 (Cp_2), 50.37 (Me). Cp_2TiCl_2 : δ 120.18.

7. The reaction *must* be quenched *into* 6% aq **ammonium chloride**, or substantial decomposition will occur. The amount of **ammonium chloride** is optimized.

8. The reaction mixture is very thick and is too viscous to flow through a standard 12-gauge cannula. The transfer is best accomplished by using 1/4" to 3/8" i.d. inert tubing (PTFE, polytetrafluoroethylene, or polypropylene) inserted through both septa. The mixture can then be transferred by applying only slight positive pressure on the reaction flask.

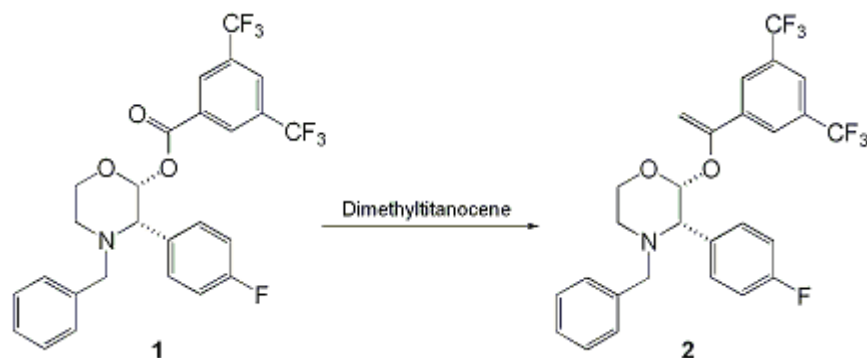
9. The workup may be done in a normal separatory funnel under air.

10. The solution must *not* be allowed to evaporate to dryness: **dimethyltitanocene** is unstable in the solid phase and could decompose with heat and gas evolution. The compound is also known to be unstable in neat solution at temperatures above 60°C. The concentration must be done at high (20 mm or less) vacuum.

11. The ^1H NMR weight percent assay is done by diluting several drops of the solution into 1 mL of CDCl_3 and running the spectrum with a 10-sec relaxation delay between pulses to ensure an accurate integration. The product Cp singlet is integrated against the **toluene** methyl singlet and any residual THF.

12. The submitters have some evidence that thermally stressed solutions of **dimethyltitanocene** are more stable when diluted with an equal volume of THF. No complete study of the long term 5°C stability of the solution has been done, but a 10 wt% solution in THF/ **toluene** can be stored for several months in the refrigerator.

13. A 50-mL, nitrogen-purged round-bottomed flask was charged with cis-ester **1** (**(2R-cis)-3-(4-fluorophenyl)-4-benzyl-2-morpholinyl 3,5-bis(trifluoromethyl)benzoate**) (2.41 g, 4.57 mmol), **dimethyltitanocene** in **toluene** (12 mL of a 20% w/w solution in **toluene**), and **titanocene dichloride** (71 mg, 0.28 mmol). The red/orange mixture was heated to 80°C and was aged in the dark for 5.5 hr, then cooled to ambient temperature. **Sodium bicarbonate** (0.60 g), **methanol** (9.6 mL) and water (0.36 mL) were added, and the mixture was heated to 40°C for 14hr. (The hot aqueous **methanol** treatment was done to decompose the **titanium** residues into an insoluble solid. The decomposition was judged to be complete when gas evolution ceased.) The green mixture was cooled to ambient temperature and the **titanium** residues were removed by filtration. The solution was evaporated under reduced pressure and flushed with **methanol**. The crude material was recrystallized by dissolving in hot (60°C) **methanol** (24 mL), cooling to ambient temperature, then adding water (7.2 mL) over 2 hr. The material was stirred for 18 hr then isolated via filtration at ambient temperature. The filtercake was washed with 25% aq **methanol** (6 mL) and the solid was dried at ambient temperature under **nitrogen**. Vinyl ether **2** (**(2R-cis)-2-[[1-[3,5-bis(trifluoromethyl)phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-benzylmorpholine**) (2.31 g, 96%) was isolated as a pale yellow solid.

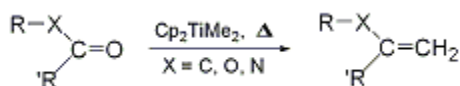


Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1996.

3. Discussion

Petasis, et al. have discovered that [dimethyltitanocene](#) is an excellent substitute for the Tebbe reagent⁴ for the methylenation of heteroatom-substituted carbonyl compounds.^{5,6}



The advantages of this reagent are its straightforward synthesis and relative air stability. The previous procedure⁷ for the synthesis of [dimethyltitanocene](#) used [methyl lithium](#) in [diethyl ether](#), which is unsuitable for large scale operations because of its extreme pyrophoricity.⁸ In addition, the method isolated the compound as a crystalline solid, which the submitters have found to be very unstable.⁹ The method described here addresses both of these concerns, and can be used to prepare multiple kilograms of the reagent.

References and Notes

1. Department of Process Research, Merck Research Laboratories, Division of Merck & Co., Inc. P. O. Box 2000, Rahway, NJ 07065.
2. Development Laboratories Merck Research Laboratories, Division of Merck & Co., Inc. Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, England.
3. A less detailed version of this procedure has been published: Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Prep. Proced., Int.* **1995**, *27*, 707.
4. (a) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270; (b) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72.
5. (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392; (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393.
6. For some applications see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron Lett.* **1990**, *31*, 6799; (b) DeShong, P.; Rybczynski, P. J. *J. Org. Chem.* **1991**, *56*, 3207; (c) Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156; (d) Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 1721; (e) Chenault, H. K.; Chafin, L. F. *J. Org. Chem.* **1994**, *59*, 6167; (f) Kuzmich, D.; Wu, S. C.; Ha, D. -C.; Lee, C. -S.; Ramesh, S.; Atarashi, S.; Choi, J. -K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943.
7. Clauss, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 8.
8. The preparation of [dimethyltitanocene](#) from [methylmagnesium iodide](#) and dichlorotitanocene in [diethyl ether](#) has been reported in a German patent. Few details of the procedure are provided, and a yield of 58% is reported. German Patent #1,037,446 (March 12, 1959) to Farbwerke

- Hoechst (*Chem. Abstr.*, **1960**, 54:18546f;).
9. For a discussion of the solid state stability of **dimethyltitanocene**, see: Erskine, G. J.; Hartgerink, J.; Weinberg E. L.; McCowan, J. D. *J. Organomet. Chem.* **1979**, 170, 51 and references therein.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Dimethyltitanocene:

Titanium, di- π -cyclopentadienyldimethyl- (8);
Titanium, bis(η^5 -2,4-cyclopentadien-1-yl)dimethyl- (9); (1271-66-5)

Titanocene dichloride: ALDRICH:

Bis(cyclopentadienyl)titanium dichloride:
Titanium, dichloro- π -cyclopentadienyl- (8);
Titanium, dichlorobis(η^5 -2,4-cyclopentadienyl-1-yl)- (9); (1271-19-8)

Methylmagnesium chloride:

Magnesium, chloromethyl- (8, 9); (676-58-4)

Chloromethyltitanocene:

Titanium, chlorodi- π -cyclopentadienylmethyl- (8);
Titanium, chlorobis(η^5 -2,4-cyclopentadien-1-yl)methyl- (9); (1278-83-7)

Benzoic acid, 3,5-bis(luoromethyl)-, (2R,3S)-3-(4-fluorophenyl)-4-(phenylmethyl)-2-morpholinyl ester
(9); (170729-77-8)

Morpholine, 2-[[1-[3,5-bis(trifluoromethyl)phenyl]ethenyl]oxy]-3-(4-fluorophenyl)-4-(phenylmethyl)-,
(2R,3S)- (9); (170729-78-9)