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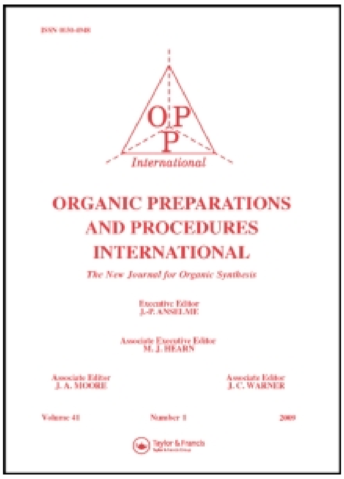

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AN IMPROVED SYNTHESIS OF DIMETHYLTITANOCENE

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AN IMPROVED SYNTHESIS OF DIMETHYLTITANOCENE

Submitted by
(07/10/95)

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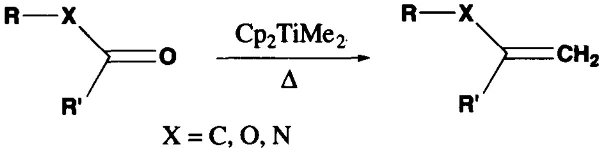
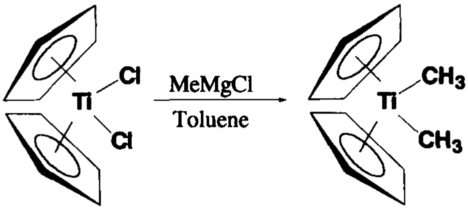
In 1990, Petasis and Bzowej reported that dimethyltitanocene (**1**) was an effective methylenating reagent for a variety of carbonyl compounds, including esters and lactones.[1]



Subsequently, the reagent was used to methylenate heteroatom-substituted carbonyl compounds,[2] and was found to be a ring-opening metathesis polymerization catalyst.[3] Thus dimethyltitanocene has become a valuable synthetic tool.[4] We required the reagent on the multi-kilogram scale for an ongoing program, and found that the published procedure was not amenable to large scale operations.[5] The protocol called for methylating titanocene dichloride with the pyrophoric methyllithium in ether, followed by an aqueous quench, and then a work-up where the material was isolated as a solid. We have found that Cp_2TiMe_2 is unstable in the solid phase, and evaporation of solutions containing the reagent decomposed unpredictably.[6] We present here a safe method for the preparation of **1** from Cp_2TiCl_2 and methyl magnesium chloride in THF.[7]



Toluene is used as the solvent and the reaction is quenched into 6% aqueous ammonium chloride. After several water and brine washes, the dried organic layer is concentrated to about half the original volume, and is assayed by NMR and used as is (typical assays 12-17 wt%). We found solutions of **1** in toluene with 10% added THF are stable at 0° for several months. This process has been run several times on a multi-kilogram scale giving yields in the 85-90% range.

EXPERIMENTAL SECTION

The ^{1}H and ^{13}C NMR spectra were measured at 250 and 62.9 MHz in $CDCl_3$. The proton spectra were run with a 10s delay between pulses for the wt% assay. Toluene was dried to less than 150 µg/mL water (by Karl Fisher titration) with 3Å sieves. Titanocene dichloride and methylmagnesium chloride were purchased from Boulder Scientific and were used as received. Standard inert atmosphere techniques were used for the reaction and the quench was done under a blanket of nitrogen. The work-up was done in a standard separatory funnel in air.

Dimethyltitanocene (1).- To a well stirred slurry of titanocene dichloride (249 g, 1.00 mol) in toluene (2.75 L) chilled to -5° (internal temp) was added MeMgCl (750 mL, 3.0M in THF, 2.25 mol) over 1 hr, while the temperature was maintained below 8°. The resulting orange slurry was aged at 0-5° for 1 hr, or until the insoluble purple Cp_2TiCl_2 had dissolved. A NMR was used to confirm reaction completion (see below), then the reaction was added over 1 hr *via* a canula into a solution of 6% aqueous ammonium chloride (700 mL), maintained at 0-5°. The organic phase was washed with cold water (3 x 575 mL) and brine (575 mL), then dried over Na_2SO_4 (220 g). The organic layer was evaporated to 1.5 Kg (internal temperature of 25° or less). Weight % assay by ^{1}H NMR showed the solution to contain 187 g product (90%, 12.5 wt% solution in toluene/THF). Typically, the material was greater than 95% pure, with only traces of the starting material and monomethyl intermediate. The solution could be further concentrated to 1.0 Kg, to a 18 wt% solution in toluene, which allowed an easier assay. Our experience, however, demonstrated that a small amount of THF increases the stability of the compound. The material was stored under nitrogen in a sealed carboy at 0°. ^{1}H NMR Cp_2TiMe_2: δ 6.05 (s, 10H), -0.05 (s, 6H). $Cp_2TiClMe$: δ 6.22 (s, 10H), 0.80 (s, 3H). Cp_2TiCl_2: δ 6.56 (s, 10H). ^{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.

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E. L. Weinberg and J. D. McCowan *J. Organomet. Chem.*, **170**, 51 (1979) and references therein.

7. 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. Abs., **54**:18546f) (1960)].

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(±)-3,4,4a,5,6,7-HEXAHYDRO-4a,7,7-TRIMETHYL-1(2*H*)-NAPHTHALENONE

Submitted by (8/21/95)
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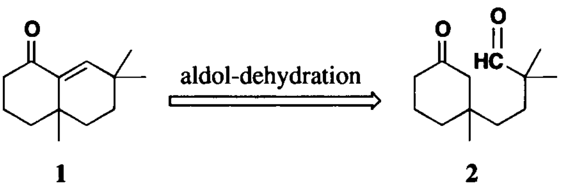
A recent photochemical study in this laboratory required the preparation of (±)-3,4,4a,5,6,7-hexahydro-4a,7,7-trimethyl-1(2*H*)-naphthalenone (**1**). Retrosynthetic analysis suggested that **1** should be readily available by intramolecular aldol condensation of (±)-2,2-dimethyl-4-(1-methyl-3-oxocyclohexyl)butanal (**2**). Precedent for this closure has appeared in earlier work describing annulations based on acid-mediated cyclization of keto acetals[1] and in a similar ring closure applied to the synthesis of a fused-ring heterocyclic natural product.[2]



We anticipated that direct preparation of the aldehyde by alkylation of isobutyraldehyde would be complicated by competing aldol processes; other possible routes would require manipulation of protecting groups and would result in a longer synthesis. Thus, it was planned to generate the aldehyde functionality by ozone cleavage of a side-chain alkene group. By use of this strategy, the title compound was prepared in three steps from 5-bromo-3,3-dimethyl-1-pentene and 3-methyl-2-cyclohexen-1-one in an overall yield of 54%.

Bromide **5** was prepared from the known 3,3-dimethyl-4-penten-1-ol (**3**)[3] via mesylate **4**[4] in an overall yield of 85%. The bromide was converted to the corresponding Grignard reagent and added to 3-methyl-2-cyclohexen-1-one at -78° in the presence of copper(I) iodide and chloro-