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Dimethyltitanocene: From Millimole to Kilomole

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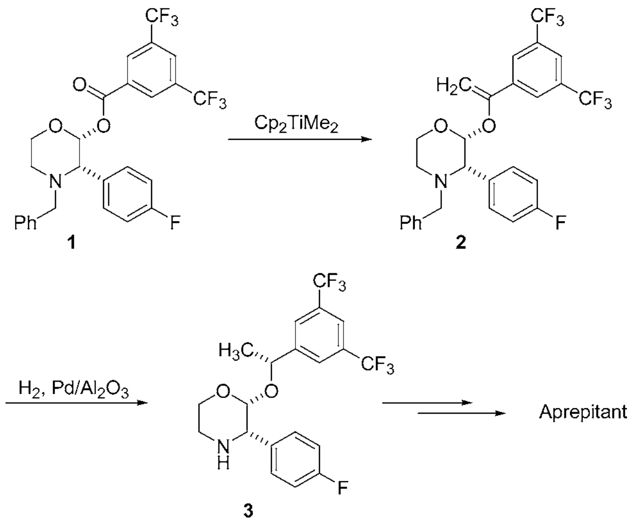
Abstract:
The process development of a dimethyltitanocene-mediated ester olefination is described. The synthetic challenges and stability issues involving large-scale production of dimethyltitanocene are documented, and the optimization of the ester olefination is detailed. The process described was used to make hundreds of kilograms of an advanced intermediate for aprepitant (Emend).

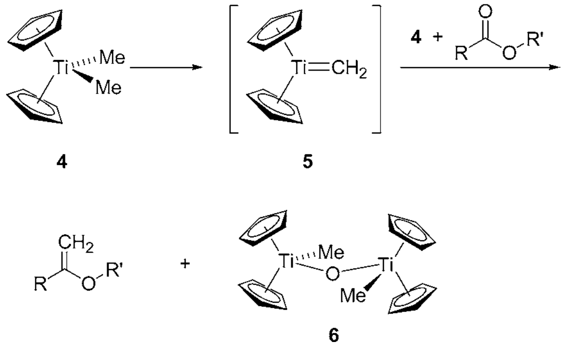
Aprepitant (Emend) is a substance P antagonist that was recently approved in the United States as a therapy to prevent chemotherapy-induced nausea and vomiting.[1] While several alternative syntheses have been described,[2] drug supplies to support the clinical program were produced via a route that employed dimethyltitanocene to convert an ester into a vinyl ether (Scheme 1).[3] The large amounts of bulk drug needed during development necessitated the production of hundreds of kilograms of dimethyltitanocene (DMT). This contribution details the efforts to make the preparation and use of this reagent safe and reliable from benchtop to 100-kg scale.

Petasis[4] developed dimethyltitanocene as a convenient alternative to the Tebbe reagent[5] and the Grubbs metalocyclobutane analogue,[6] for the olefination of esters, ketones, and amides. The advantages of DMT over the earlier reagents were ease of preparation, absence of Lewis-acidic aluminum byproducts, and importantly for the organic synthetic chemist, air and water stability. DMT is very effective at small-scale olefination transformations; indeed, the reaction depicted in Scheme 1 proceeded in near quantitative yield.

Scheme 1



Scheme 2



While the Petasis reagent is extremely effective at ester olefinations, a series of drawbacks rapidly became apparent as scale-up was contemplated. DMT is not stable in the solid state,[7] and a crystalline mass of the material would decompose, releasing heat and gas. In addition, the molecule is intrinsically unstable at synthetically relevant temperatures and concentrations, raising considerable safety concerns.[8] Since two moles of DMT are needed per mole of ester (Scheme 2),[9] not only are large amounts of the reagent needed for pilot-scale production, but an efficient method for removing the titanocene residues also had to be devel-

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oped. These and other issues were addressed during the development of the synthetic process for DMT production and the refinement of the olefination reaction.

The literature procedure for making DMT[10] consisted of treating a slurry of titanocene dichloride in MTBE/toluene with methyllithium in ether. Then, after aqueous workup, the material was isolated as an orange crystalline solid by evaporation to dryness. The reagent was then redissolved in THF or toluene and used in the desired olefination reaction. Probe-scale investigations showed that the solid DMT would decompose in minutes upon reaching dryness, turning black with gas evolution. A protocol was developed where the material was kept in solution throughout workup, then the solution was dried with sodium sulfate, and carefully solvent-switched and concentrated to a ∼20 wt % solution. This produced the first 1.5 kg of DMT, which was immediately used to olefinate 1 kg of ester. The vinyl ether was isolated via an extremely tedious trituration with hexane, then the remaining titanocene residues were decomposed with hydrogen peroxide.

The problems uncovered during the first kilogram-scale run spurred considerable efforts into improving the DMT synthesis and ester olefination. The first issue addressed was replacement of the hazardous methyllithium in ether with methyl Grignard reagent in THF. The reaction was unaffected by the change in methylating reagent; however, the aqueous workup of the DMT formed from MeMgCl proved problematic. It was discovered that if water was added to a mixture of DMT and $MgCl_2$, substantial amounts of the DMT reverted back to titanocene dichloride and methyltitanocene chloride. The issue was addressed by doing a reverse quench of the DMT/$MgCl_2$ reaction mixture into buffered water. Optimization led to the reaction being run in toluene, with a workup employing 6% ammonium chloride. The DMT solution was then dried by azeotropic vacuum distillation and concentrated to 15−20 wt %.

While optimizing the preparation of DMT, we noticed that reagent samples containing small amounts of methyltitanocene chloride ($Cp_2TiMeCl$) gave cleaner and higher-yielding olefination reactions. Even more dramatic was the cleaner formation of the oxo-bridged titanocene dimer byproduct **6** (Scheme 2), which would become more important as we contemplated recycling the titanium (see below). These observations led to a procedure in which a few mole percent of titanocene dichloride was added to the DMT solution, giving methyltitanocene chloride by metathesis, prior to the olefination reaction.

Finally, an efficient titanocene removal protocol was needed before further scale-up could be done. It was found that heating the spent reaction mixture with aqueous methanol decomposed the titanium to an easily filterable solid. To protect the vinyl ether from acid-catalyzed decomposition, and to prevent polymerization of cyclopentadiene, sodium bicarbonate was added to maintain a slightly basic environment. After removal of the Ti residues and bicarbonate, the product was isolated from *n*-propanol/water as an off-white crystalline solid.

The improved protocol was employed in multiple kilogram-scale runs without incident. Before introduction into pilot-plant scale however, operational hazard testing revealed a substantial risk of unsafe operating conditions during the concentration of DMT. The potential for a large exotherm with substantial pressure increase was considered unacceptable on the multikilogram scale. It is believed that in the absence of a substrate, the carbene (**5**) formed from heating DMT reacts with additional DMT, leading to heat and gas evolution.[8] This issue was addressed by adding the ester substrate to the titanocene reagent before concentration, so that any carbene formed would be trapped in the desired reaction. The process was successfully introduced into the pilot plant.

In contemplating longer-term development, the limitations of the first-generation pilot-plant protocol became apparent. Two main issues required resolution: the workup of the dimethyltitanocene-formation reaction mixture, which gave emulsions that lowered yields to 80%, and a relatively narrow end of reaction window for the olefination. Additionally, the production cost issue took on greater importance as factory introduction approached.

The emulsion problem encountered in the DMT workup was caused by the presence of gummy solids, which entrained DMT-containing organic phase into the aqueous cut. While this was not a serious issue on kilo scale, where it was convenient to observe the phase interface in a glass vessel, in larger vessels the separation became difficult.

The solids issue was resolved by filtering the DMT mixture prior to phase separation. To the quenched aqueous organic mixture of DMT was added Celite (diatomaceous earth), and the entire batch was filtered through a filter press. The resulting clear organic and aqueous phases were easily separated, and the organic phase was worked up with minimal losses. To improve volumetric efficiency, the initial reaction solvent was changed to THF (doubling the concentration), while the quench mixture contained toluene, Celite, and aqueous ammonium chloride. The largest runs using this protocol produced 235 kg (87%) of dimethyltitanocene per batch.

The end of reaction window was more challenging. While the olefination reaction typically went to 98% assay yield within 5 h at 80 °C, the yield would then drop by as much as 10% if heating continued for a further 30 min. The time required to sample, assay, and cool a large-scale reaction made catching the end of reaction difficult. While we considered in situ reaction monitoring, ultimately we developed a chemical solution.

The source of the problem was the excess DMT required to complete the reaction within a reasonable time. When the ester substrate is present, the titanium carbene reacts with it in a controlled fashion. Once the ester is consumed, the carbene reacts by other pathways which decompose the vinyl ether product. What was needed was another reagent to take over when the ester **1** was consumed, providing an alternative reaction pathway. Ideally this reagent should react more slowly than **1** so that it does not interfere with the desired reaction.

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[10] Claus, K.; Bestian, H. *Ann.* **1962**, *654*, 8.

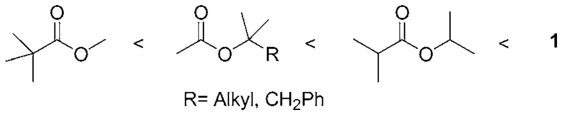

Figure 1. **Relative reactivity of esters toward 5.**

Scheme 3

$$\begin{tikzcd} Cp_2TiCl_2 \arrow[rr, "MeMgCl"] & & Cp_2TiMe_2 \arrow[dl, "1"] \\ & (Cp_2TiMe)_2O \arrow[ul, "HCl"] & \end{tikzcd}$$

A series of esters with differing steric properties was screened for this use. The overall rate of reaction is determined by rate-limiting formation of the reactive carbene **5**, and so it is the same for all the esters.[9] However, competition experiments between esters revealed relative rates (Figure 1). Acetates of tertiary alcohols were found to have the desired properties, reacting rapidly enough to protect the vinyl ether, but slowly enough to avoid competing with the substrate ester **1**. From this class, the inexpensive ester 1,1-dimethyl-2-phenylethyl acetate was selected.[11] An optimized 0.75 equiv (relative to **1**) was added to the reaction mixture from the beginning, allowing complete conversion of **1** to vinyl ether **2** in 5 h, and protecting **2** for as much as 24 h of additional heating.

Finally, a method to recycle spent DMT was desired to reduce raw material costs and minimize the solid waste generated. As shown in Scheme 2, the byproduct formed from the olefination reaction was the oxo-bridged titanocene dimer **6**. The dimer could be crystallized and recovered in 80% yield by concentrating the toluene reaction mixture and adding heptane. Treatment of the isolated oxo-dimer with HCl in toluene or THF converted it to crystalline titanocene dichloride which was isolated by filtration in 94% yield.[12] Since titanocene dichloride is the precursor to DMT, this closes the recycle loop (Scheme 3.) After recovery of the dimer, the remaining titanium in the olefination reaction mixture was removed by decomposition as before, and the vinyl ether **2** was crystallized from ethanol/water in 91% yield.

The technical challenges of the large-scale synthesis and use of DMT were overcome by a team effort involving chemists, engineers, and safety experts. This work demonstrates that the production and use of technically challenging organometallic reagents is feasible in pharmaceutical manufacturing.

Experimental Section

A laboratory-scale procedure for the synthesis of dimethyltitanocene[13] and a titration method for its quantitative analysis[14] have been published. All reagents were purchased from commercial sources and were used without purification. THF was obtained with a moisture content of <100 ppm, or it was dried with molecular sieves before use. Ethanol was denatured with 5% toluene. All operations were carried out under an atmosphere of dry nitrogen.

(2*R*,3*S*)-4-Benzyl-2-({1-[3,5-bis(trifluoromethyl)phenyl]-vinyl}oxy)-3-(4-fluorophenyl)morpholine (2). In a 1000-gal glass-lined vessel, a slurry of titanocene dichloride (334 kg, 1.35 kmol) in THF (1000 L) was chilled to −5 to −10 °C, then methylmagnesium chloride (1020 kg, 3 M in THF, 3.03 kmol) was charged over 5.5 h, maintaining the temperature below 5 °C. The Grignard reagent was rinsed in with additional THF (17 L), and the mixture was stirred at −1 to −9 °C for 1.5 h, during which time the remaining titanocene dichloride dissolved. Completion of the reaction was confirmed by ^{1}H NMR.

In a 1500-gal vessel, a quench mixture was prepared by charging water (1170 L), ammonium chloride (160 kg), Celite (84 kg), and toluene (1500 L). The mixture was chilled to 0 to −5 °C, then the dimethyltitanocene process stream was added over 2.5 h, rinsing in with additional THF (113 L). The quench mixture was maintained below 6 °C. The mixture was then filtered (9.2 m^2 filter press), rinsing with THF (170 L) and toluene (590 L). The biphasic system was allowed to settle, and the lower aqueous phase was removed. The organic phase was washed with water (1340 L). The batch temperature was maintained at 0−10 °C throughout the workup.

A portion of the batch (~2700 L) was transferred to a 1000-gal vessel, and ester **1** (250 kg, 474 mol) was added. The solution was vacuum distilled with a maximum temperature of 35 °C to a volume of 1200 L. The remaining unconcentrated material was then introduced into the distillation vessel followed by a toluene flush (200 L). The batch was reconcentrated to 1200 L, and the solution was assayed to contain 20 wt % dimethyltitanocene in a molar ratio of 2.4 to 1 vs the cis ester, for an 85% yield.

Titanocene dichloride (7.3 kg, 29 mol) was added, followed by 1,1-dimethyl-2-phenethyl acetate (70 kg, 355 mol), and the orange solution was heated to 80 °C for 6.5 h. HPLC assay showed complete consumption of the starting ester. The mixture was cooled to 25 °C and then vacuum concentrated to a volume of 780 L, keeping the temperature below 30 °C. The crystallized titanium byproduct $(Cp_2TiMe)_2O$ (**6**) was further precipitated by adding heptanes (723 kg) over 2 h and then collected by filtration and washed with heptanes (795 kg).

The filtrate was concentrated to 875 L via vacuum distillation at 10−20 °C. The remaining titanium residues were then quenched by adding sodium bicarbonate (60 kg), ethanol (415 kg), and water (48 kg), and then heating to 60 °C for 6 h. The volatile organic gases generated in the quench were efficiently scrubbed via a thermal oxidizing unit. The slurry was cooled to 20 °C, and the inorganic residues were removed by filtration, rinsing with toluene (260 kg).

The filtrate was then vacuum concentrated at 20−25 °C to a volume of 750 L and then the solvent was switched to ethanol via a constant volume distillation. When the solution contained <2% toluene by volume, the distillation was

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[11] Huffman, M. A. U.S. Patent 6,255,550, 2001.

[12] Huffman, M. A.; Payack, J. F., U.S. Patent 6,063,950, 2000.

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stopped. Further ethanol was added (286 kg) and then the vinyl ether was further crystallized by the addition over 1 h of 50% aqueous ethanol (prepared from 432 kg of ethanol and 550 kg of water). The product was collected in a centrifuge filter, with a 380-L wash of 2:1 ethanol water, then dried under vacuum at 45 °C. Yield 227 kg of vinyl ether (91%): ^{1}H NMR (400 MHz, $CDCl_3$) 2.42 (dt, $J = 3.6$, 12.0, 1H), 2.90 (d, $J = 12.0$, 1H), 2.91 and 3.94 (ABq, $J = 13.6$, 1H), 3.62−3.66 (m, 1H), 3.72 (d, $J = 2.6$, 1H), 4.09 (dt, $J = 2.4$, 12.0, 1H), 4.75 (d, $J = 3.2$, 1H), 4.82 (d, $J = 3.2$, 1H), 5.32 (d, $J = 2.6$, 1H), 7.09 (t, $J = 8.8$, 2H), 7.24−7.33 (m, 5H), 7.58−7.62 (m, 2H), 7.80 (s, 1H), 7.90 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) 51.4, 59.5, 60.2, 69.4, 89.8, 96.8, 115.5 (d, $J_{CF} = 20$), 121.9 (m), 123.5 (q, $J_{CF} = 272$), 125.8, 127.5, 128.4, 128.7, 130.6, 131.2 (q, $J_{CF} = 40$), 133.4, 137.7, 138.6, 155.0, 162.2 (d, $J_{CF} = 241$). Anal. ($C_{27}H_{22}F_7NO_2$) Calc: C, 61.72; H, 4.22; N, 2.67; F, 25.31. Found: C, 61.79; H, 4.10; N, 2.65; F, 25.27.

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