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STABLE AND CONVENIENT ALKYLTITANIUM REAGENTS FOR ORGANIC SYNTHESIS

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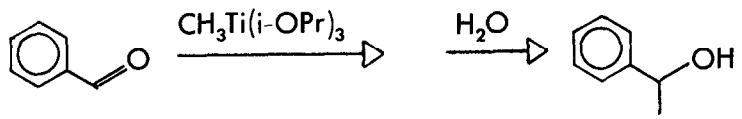
Monocyclopentadienyl titanium alkyls perform similarly to other alkyltitanium reagents in reactions with carbonyl groups while possessing significantly greater thermal stability.

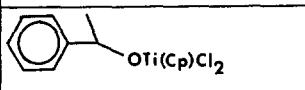
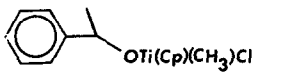
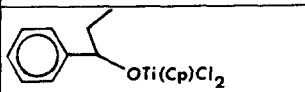
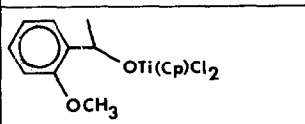
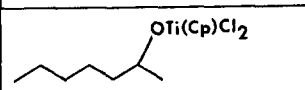
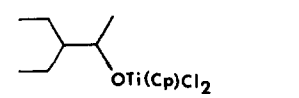
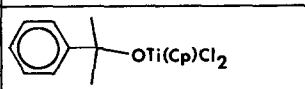
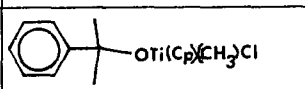
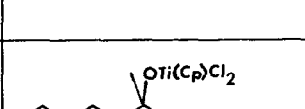
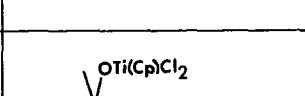
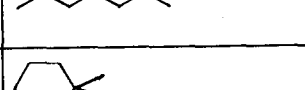
Synthetic applications of organotitanium compounds have been receiving attention recently because of the exceptional selectivity exhibited by many of these compounds in their reactions with carbonyl groups. Addition reactions with aldehydes and ketones have been particularly successful and are well documented[1,2]. Subsequent hydrolysis of the adduct produces the corresponding alcohol, as for example in [3]



The main inconvenience in using these reagents has been their thermal instability. The advantages of finding reagents which are more stable, particularly for those alkyls having a hydrogen on a β-carbon, have already been enumerated [2].

Recently, $CpTi(CH_3)Cl_2$ [4] has been shown to combine reasonable reactivity with high thermal stability [5]. We now report preliminary studies showing that this reactivity extends to the aldehyde and ketone reactions noted above. The reactions have been monitored conveniently in flame-sealed NMR tubes prepared under a nitrogen atmosphere within a glove box. Concentrations of the substrate were 0.2 mol L^{-1}. Reagent to substrate ratios were usually 1.1:1 but were varied up to 4:1 in some cases. Reaction times of from thirty minutes up to a few hours were achieved at room temperature with aldehydes, and at 50°C with most ketones. Hydrolysis of the addition product gave the corresponding alcohol. In larger scale syntheses, the use of wet hexane to carry out the hydrolysis produced the alcohol without producing a separate aqueous phase. The titanium products precipitate and are easily separated by filtration. The alcohol can then be isolated by distillation or other means, depending on the alcohol.

CD_2Cl_2 was the solvent in most cases, since $CDCl_3$ causes a significant loss of reagent through formation of $CpTiCl_3$, requiring a 20% excess of reagent in reactions with aldehydes and a threefold excess in reactions with ketones. Results are summarized below.

Substrate Reagent	Product	NMR Data for Products[6] Notes and Comment
benzaldehyde $CpTi(CH_3)Cl_2$	 1	CD_2Cl_2; Cp 6.60, H 5.84, CH_3 1.65, J_{CH_3-H} 6.58 $CDCl_3$; Cp 6.70, H 5.76, CH_3 1.63 Yield 95%
benzaldehyde $CpTi(CH_3)_2Cl$	 2	$CDCl_3$; Cp 6.28, H 5.67, CH_3 1.63 CH_3(on Ti) 1.15; reagent:substrate 1:1
benzaldehyde $CpTi(C_2H_5)Cl_2$	 3	$CDCl_3$; Cp 6.55, H 5.55, CH_2 1.80, CH_3 1.00 Yield 90%
o-methoxy- benzaldehyde $CpTi(CH_3)Cl_2$	 4	CD_2Cl_2; Cp 6.63, H 6.30, CH_3 1.60, CH_3O 3.89 J_{CH_3-H} 6.54 Yield 90%
hexanal $CpTi(CH_3)Cl_2$	 5	CD_2Cl_2; Cp 6.72, H 4.81, CH_3 1.36, J_{CH_3-H} 6.0 Yield 85%
2-ethylbutanal $CpTi(CH_3)Cl_2$	 6	CD_2Cl_2; Cp 6.72, H 4.94, CH_3 0.95, J_{CH_3-H} 6.6 Yield 85%
acetophenone $CpTi(CH_3)Cl_2$	 7	CD_2Cl_2; Cp 6.75, CH_3 1.81 $CDCl_3$; Cp 6.55, CH_3 1.79 Yield 60%
acetophenone $CpTi(CH_3)_2Cl$	 8	$CDCl_3$; Cp 6.35, CH_3 1.78, CH_3(on Ti) 1.15 $C_6H_5C(CH_3)_3$ also forms, becoming dominant product at reagent:substrate > 2
2-heptanone $CpTi(CH_3)Cl_2$	 9	CD_2Cl_2; Cp 6.72, CH_3 1.42 Requires one day at 50°C. Many by-products form at 70°C.
4-heptanone $CpTi(CH_3)Cl_2$	 10	CD_2Cl_2; Cp 6.72, CH_3 1.39 Requires two day at 50°C. Many by-products form at 70°C.
cyclohexanone $CpTi(CH_3)Cl_2$	 11	CD_2Cl_2; Cp 6.91, CH_3 1.43 Requires 12 hour at 50°C. Some by-products.
benzoyl chloride $CpTi(CH_3)Cl_2$	as 7	Yield 50%. Requires reagent:substrate ratio of 2:1. Very slow.
benzoyl chloride $CpTi(CH_3)_2Cl$	as 7,8	Requires reagent:substrate ratio of 2:1. Complete in one hour at room temperature.

Note that $CpTi(CH_3)Cl_2$ reacts with the acid chloride, giving first the ketone and then, through addition of a second reagent molecule, the addition product. Reaction rates for the two steps are similar, and the adduct spectrum appears soon after that of acetophenone. This reaction cannot be carried out using $CH_3Ti(i\text{-}OPr)_3$ which transfers an isopropoxy group rather than a methyl.

$CpTi(CH_3)_2Cl$ reacts with acetophenone to give an addition product, (8), but even at a 1:1 ratio of reagent to substrate, a little $C_6H_5C(CH_3)_3$ is observed. Increasing ratios of reagent to substrate produce increasing proportions of $C_6H_5C(CH_3)_3$ to adduct. Thus $CpTi(CH_3)_2Cl$ produces the direct geminal dimethylation of ketones previously reported for the very much less stable reagent $(CH_3)_2TiCl_2$ [1,2,7]. In the case of reacting $CpTi(CH_3)_2Cl$ with benzoyl chloride (at a reagent to substrate ratio of 2:1), both (7) and (8) are formed in a few hours at room temperature with very little $C_6H_5C(CH_3)_3$ appearing. Although the intermediate acetophenone is detected, it is never present in large quantities.

Some tests of selectivity have been made, using solutions originally 0.1 mol L^{-1} in reagent and in each substrate. Solvent is CD_2Cl_2. Results are as follows.

Substrates	Product	$CpTi(CH_3)Cl_2$	$CH_3Ti(i\text{-}OPr)_3$
benzaldehyde, acetophenone	(1):(7)	>99:1	>98:2 [3]
2-ethylbutanal, 2-heptanone	(6):(9)	>99:1	----
benzaldehyde, o-methoxybenzaldehyde	(1):(4)	20:80	13:87 [1]
hexanal, 2-ethylbutanal	(5):(6)	90:10	92:8 [8]
2-heptanone, 4-heptanone	(9):(10)	75:25	85:15 [1]
cyclohexanone, 4-heptanone	(11):(10)	90:10	97:3 [1]

In sum, these tests indicate that $CpTi(CH_3)Cl_2$ is not as convenient as $CH_3Ti(i\text{-}OPr)_3$ in reactions with ketones but is more convenient in reactions with aldehydes. With ketones the long reaction times and higher temperatures produce more by-products, lower yields and less efficient use of reagents. With aldehydes on the other hand, $CpTi(CH_3)Cl_2$ reacts smoothly at room temperature. It exhibits essentially total selectivity in competitions between aldehydes and ketones, with no side products evident. In the case of the ethyl analogue, the convenience of thermal stability may make it attractive even in some reactions with ketones and this is also true of the dimethylation reaction using $CpTi(CH_3)_2Cl$. Finally, in the case of reactions with the acid chloride, the monocyclopentadienyl reagents have a unique advantage since alkoxy reagents substitute an alkoxy instead of an alkyl.

Most of the benefits of these reagents relate to their thermal stability. If shielded from light and under an inert atmosphere, $CpTi(CH_3)Cl_2$ can be purified, transported and stored indefinitely without refrigeration [5] whereas $CH_3Ti(i\text{-}OPr)_3$ requires refrigeration in order to store it for "at least a month" [3] and other monomethyl reagents are less stable still. The margin of stability is even greater in the case of reagents having hydrogen on a β-carbon, and in the case of dialkyls. Many such reagents must be freshly prepared and used at

low temperatures [1,2]. In contrast, $CpTi(C_2H_5)Cl_2$ is stable for several weeks providing that it is kept below its melting point of 20°C. $CpTi(CH_3)_2Cl$, although it requires refrigeration for long-term storage, can be used in a glove box for hours and then returned to refrigeration without significant decomposition.

Synthesis of $CpTi(CH_3)Cl_2$ itself is carried out most cheaply using CH_3Li or CH_3MgCl but most conveniently using $(CH_3)_2Zn$ [5]. The previously published method can be simplified further by omitting the filtration step and, after evaporation of the solvent, subliming directly from the residue at 55°C to a cold finger at 5°C. The yield is 71% based on $CpTiCl_3$. The preparation of $CpTi(C_2H_5)Cl_2$ is analagous, with the final sublimation step being done at 35°C and the red crystals collected at 0°C. Yield is 65%.

$CpTi(CH_3)_2Cl$ is prepared by the addition over a ten minute period of 23.9 mmol of CH_3MgCl in 9 mL of tetrahydrofuran to 3.00 g (13.7 mmol) of $CpTiCl_3$ dissolved in 50 mL of toluene at room temperature. Addition of the Grignard causes the solution to change from orange to yellow and a white precipitate forms. The solution is stirred for 10 minute and allowed to settle for 1 hour. It is then cooled to 0°C and the solvent removed by pumping. A cold finger at 0°C is inserted and the flask brought to room temperature. Yield of the orange crystals is 42% based on $CpTiCl_3$. Despite the stoichiometric excess of $CpTiCl_3$, the product sometimes contains traces of $CpTi(CH_3)_3$. Where this occurs, the impurity can be converted to the desired product by adding the appropriate amount of $CpTiCl_3$ in solution and stirring until equilibration.

NMR data for these three reagents are as follows, all for 0.2 mol L^{-1} solutions in $CDCl_3$ at 25°C. Chemical shifts are in ppm relative to TMS and coupling constants are in Hz.

$CpTi(CH_3)Cl_2$: Cp δ_H 6.71, δ_C 118.97, J_{C-H} 178; CH_3 δ_H 1.93, δ_C 80.99, J_{C-H} 131

$CpTi(CH_3)_2Cl$: Cp δ_H 6.48, δ_C 115.64, J_{C-H} 174; CH_3 δ_H 1.39, δ_C 70.50, J_{C-H} 125

$CpTi(C_2H_5)Cl_2$: Cp δ_H 6.66, δ_C 118.90, J_{C-H} 179; CH_2 δ_H 2.54, δ_C 104.65, J_{C-H} 128; CH_3 δ_H 1.63, δ_C 22.12, J_{C-H} 127; CH_3CH_2 J_{H-H} 7.3

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6. In the NMR data, the H listed for aldehyde addition products is that on the carbon bearing the oxygen. The methyl and ethyl listed are those added by the reagent unless otherwise indicated. All are relative to TMS.
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