Direct Geminal Dimethylation of Ketones using Dimethyltitanium Dichloride

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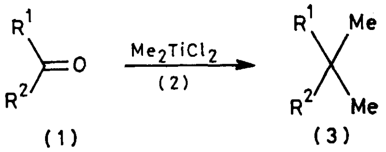
Summary Ketones are readily converted into the corresponding geminal dimethyl derivatives on reaction with dimethyltitanium dichloride under mild conditions; tertiary alcohols react similarly.

THE geminal dimethyl structural unit occurs frequently in terpenes, steroids, and other compounds of practical and theoretical interest.[1] The formal replacement of oxygen in ketones by two methyl groups is an attractive synthetic strategy.[2] We have recently shown that this is possible in a three-step process involving Grignard addition followed by conversion into the tertiary alkyl halide and subsequent reaction with $MeTiCl_3$,[3] Me_2TiCl_2,[3] or Me_2Zn.[4] This sequence is milder and more efficient than the previous procedure of Meisters and Mole, in which ketones or tertiary alcohols are pyrolysed with a large excess of trimethylaluminium in a closed vessel at 120—180 °C.[5] We now report that exhaustive methylation of ketones and tertiary alcohols is possible under mild conditions using organotitanium chemistry. The reaction of the ketone (**1**) (1 equiv.) and dimethyltitanium dichloride (**2**) (2 equiv.) in methylene dichloride in the temperature range −30 to 22 °C (method A) affords high yields of the desired products (**3**). Alternatively, a two-step sequence involving the reaction of Me_2TiCl_2 and the ketone at −30 °C (20 min) followed by addition of $TiCl_4$ and Me_2Zn (1 equiv. each) in rapid succession and allowing the mixture to come to room temperature (method B) is also successful and in some cases more satisfactory. Both methods require an excess of two methyl groups in the organometallic reagent in order to achieve maximum yields.



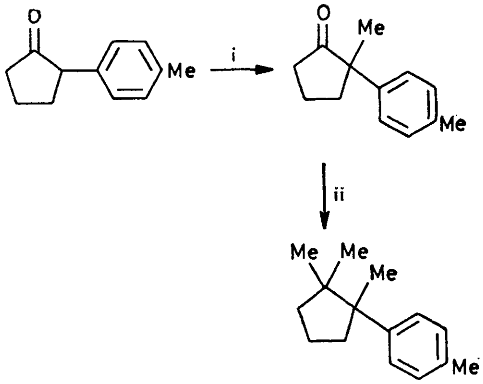
(1) (3)

Table 1. Direct geminal dimethylation of ketones.

Ketone (**1**)	Method	% Yield (isolated) of (**3**)
Heptan-4-one	B	68
Dicyclopropyl ketone	B[a]	84
5-Chloropentan-2-one	B	82
1-Adamantyl methyl ketone	B	58
Benzophenone	A[a]	83
Cyclohexanone	A	70
,,	B	72
Cyclododecanone	B	73
Indan-1-one	A[a]	86
Thiochromanone	A[a]	77
4,5,6,7-Tetrahydrobenzo-[*b*]thiophen-4-one	B[a]	74

[a] 15 min at −50 °C followed by 30 min at −10 °C. In all other cases the components were brought together at −30 °C and the mixture was allowed to come to room temperature.

Table 1 shows that a variety of structurally different ketones undergo smooth geminal dimethylation, including those which lead to products having two neighbouring quarternary carbon atoms. Noteworthy is the fact that undesired side reactions such as rearrangement, elimination, or enolization, which are known to occur with trimethylaluminium,[5] are essentially absent. Our process is of particular value when the corresponding tertiary alkyl halide is extremely sensitive or difficult to prepare as in the case of 4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-one.[6] Functional groups such as sulphides, thiophen, aromatic components, and primary alkyl chlorides are tolerated. Chemoselectivity is also observed when a 1:1 mixture of cyclohexanone and ethyl acetate is treated according to our procedure, the titanium reagent reacting only with the ketone.



Scheme. i, NaH, glyme, 0 °C, MeI (93%); ii, method A or B (33—34%).

A useful application of the method is exemplified by the synthesis of cuparene, a terpene having two neighbouring quaternary carbon atoms in a cyclic array[7] (Scheme). The yield of isolated product in the critical step is only 34% (50% conversion), but the simplicity of the method underlines its value. The mechanism of the reaction involves Grignard-type addition of dimethyltitanium dichloride to the ketone function.[8] The tertiary titanium alcoholate is then methylated by further organometallic reagent, very likely *via* intermediate carbonium ions.

It is interesting to note that Me_3Al in combination with $AlCl_3$ fails to induce geminal dimethylation.[8] In contrast, a mixture of cyclohexanone (1 equiv.), Me_3Al (2 equiv.), and $TiCl_4$ (2 equiv.) at −30 °C to room temperature (2 h) causes 70% conversion into 1,1-dimethylcyclohexane together with 30% of 1-methylcyclohexene. Thus, the high affinity of titanium for oxygen-containing functionality seems to be the critical factor in these reactions.

We have also accomplished the methylation of tertiary alcohols. $TiCl_4$ (1 equiv.) was added to the alcohol (1 equiv.) in methylene dichloride at −30 to −40 °C and after 5–10 min the mixture was treated with Me_2Zn (1 equiv.) for *ca.* 1 h (Table 2). Me_2TiCl_2 can also be used directly. Noteworthy is the smooth double methylation of 2,5-dimethylhexane-2,5-diol.

For the preparation of Me_2TiCl_2, various organometallic precursors can be mixed with $TiCl_4$.[9] We allowed equiva-

Table 2. Methylation of tertiary alcohols.

Alcohol	Product	% Yield (isolated)
2-Methylpentan-2-ol	2,2-Dimethylpentane	>90[a]
1-Butylcyclohexan-1-ol	1-Butyl-1-methylcyclohexane	74
1-Methyl-4-t-butylcyclohexan-1-ol	1,1-Dimethyl-4-t-butylcyclohexane	74
2-Methyladamantan-2-ol	2,2-Dimethyladamantane	79
2,5-Dimethylhexane-2,5-diol	2,2,5,5-Tetramethylhexane	73

[a] Yield in this case determined by ^1H n.m.r. spectroscopy.

lent amounts of Me_2Zn and $TiCl_4$ in dry methylene dichloride to react at −30 °C for 30 min under nitrogen. The mixture contains about 90% of Me_2TiCl_2, and can be used without further purification.

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[1] For a review of procedures for preparing compounds having quaternary carbon atoms, see S. F. Martin, *Tetrahedron*, 1980, **36**, 419.

[2] The hydrogenolysis of certain cyclopropanes derived from ketones yields compounds containing geminal dimethyl groups: C. Gröger, H. Musso, and I. Rossnagel, *Chem. Ber.*, 1980, **113**, 3621; W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, 1978, **100**, 2583.

[3] M. T. Reetz, J. Westermann, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 900.

[4] M. T. Reetz, B. Wenderoth, R. Peter, R. Steinbach, and J. Westermann, *J. Chem. Soc., Chem. Commun.*, 1980, 1202.

[5] A. Meisters and T. Mole, *Aust. J. Chem.* 1974, **27**, 1665.

[6] Although methylmagnesium iodide adds to this ketone, various attempts to prepare the corresponding tertiary chloride failed: R. Steinbach, Diplomarbeit, Universität Bonn, 1980.

[7] For an excellent review of terpenes including cuparene syntheses up to 1972 see: C. H. Heathcock in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Vol. II, Wiley, New York, 1973; C. W. Bird and Y. C. Young, *Synthesis*, 1974, 27; O. P. Vig, R. K. Parti, K. C. Gupta, and M. S. Bhatia, *Indian J. Chem.*, 1973, **11**, 981.

[8] M. T. Reetz and J. Westermann, unpublished results.

[9] Gmelin, 'Handbuch Anorganische Chemie,' vol. 40, Springer Verlag, Berlin–Heidelberg–New York, 1977, p. 71.

[10] Previously hexane was used as the solvent: K. H. Thiele, P. Zdunneck, and D. Baumgart, *Z. Anorg. Allg. Chem.*, 1970, **378**, 62.