Stereochemical Evidence for a Carbonium Ion Rearrangement during Reaction of Dimethyltitanium Dichloride with a Ketone

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Racemization during the reaction of dimethyltitanium dichloride with the 2,2-disubstituted cyclopentanone (−)-(**3**) of high enantiomeric purity provides stereochemical evidence for a carbonium ion rearrangement during this dimethylation process.

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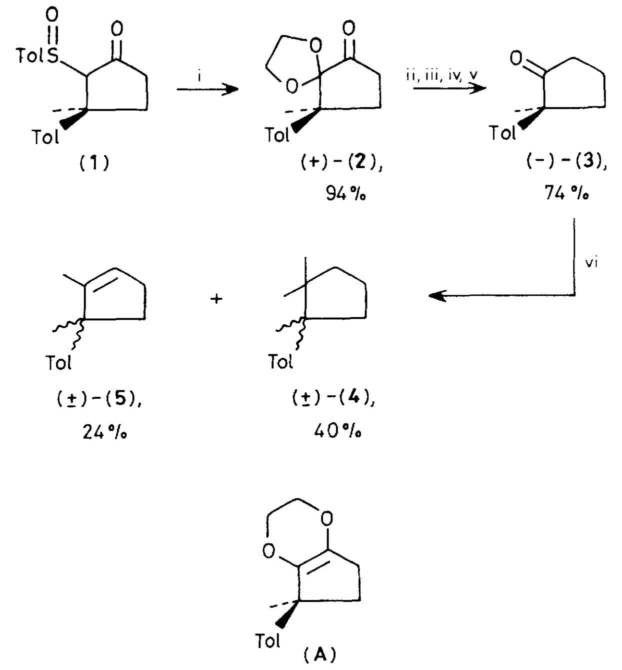
gem-Dimethylation of carbonyl groups ($>C{=}O \rightarrow >CMe_2$) is an important transformation that has attracted much interest,[1] especially as a method of preparing valuable and synthetically challenging quaternary carbon centres.[2] The most recent and direct method for accomplishing this exhaustive methylation of a ketone carbonyl group uses some new organotitanium reagents, especially dimethyltitanium dichloride.[3] Reetz has developed this new synthetic method, demonstrating that this reaction proceeds *via* initial organometallic addition to the carbonyl carbon atom to form a tertiary titanium alcoholate which then reacts with more methyltitanium reagent 'very likely *via* intermediate carbonium ions;'[3a] carbonium ion rearrangement products, however, have not been reported. This dimethylation process has been applied to a preparation of racemic cuparene,[3a] a terpene having two *vicinal* quaternary carbon centres. We have repeated Reetz's synthesis of cuparene using the ketone (−)-(**3**) of high enantiomeric purity to determine whether dimethylation using dimethyltitanium dichloride proceeds in this case with a 1,2-Wagner–Meerwein rearrangement which would destroy the chirality of the system and, therefore, which would produce racemic products.

The key cyclopentanone (−)-(**3**) of 76% enantiomeric purity was prepared by the method in Scheme 1. The optically active β-keto sulphoxide (**1**), available from our project on asymmetric total synthesis of (+)-α-cuparenone,[4] underwent an unusual Pummerer rearrangement with ethylene glycol and toluene-*p*-sulphonic acid to produce the acetal ketone (+)-(**2**).[5] Carbonyl reduction, formation of a dithiocarbonate from the resulting secondary alcohol, tri-n-butyltin hydride reduction,[6] and acetal hydrolysis led to the 2,2-disubstituted cyclopentanone (−)-(**3**), $[\alpha]_D^{25}$ −60.2° (*c* 2.68, $CHCl_3$). Reaction of ketone (−)-(**3**) with dimethyltitanium dichloride according to the



Tol = p-$MeC_6H_4SO_2$

Scheme 1. *Reagents:* i, $HOCH_2CH_2OH$, H^+; ii, $NaBH_4$; iii, NaH, CS_2, MeI; iv, $Bu^n{}_3SnH$; v, $CuCl_2$, H_2O, EtOH; vi, Me_2TiCl_2 (2 equiv.), CH_2Cl_2.

Reetz procedure† produced *racemic* cuparene (**4**) (40%)[7] and the racemic cyclopentene (**5**) (24%),‡ isolated by preparative gas chromatography.

This is the first direct experimental evidence of a hitherto undetected, degenerate carbonium ion rearrangement during dimethyltitanium dichloride reaction with a ketone. Whether this is a general phenomenon or is limited to some ketone carbonyl groups flanked by quaternary carbon centres bearing an aryl group remains to be established. In any case, the racemization observed in our dimethylation of optically active ketone (−)-(**3**) clearly indicates that care must be taken when using dimethyltitanium dichloride with ketones in which Wagner–Meerwein shifts can lead to unwanted by-products.

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† Typical procedure: $TiCl_4$ (0.65 mmol) in dry CH_2Cl_2 (1 ml) at −25 °C under argon was treated with neat Me_2Zn (0.65 mmol, ref. 8). After stirring for 0.5 h at −25 °C, a solution of (−)-(**3**) (0.27 mmol) in CH_2Cl_2 (0.15 ml) was added dropwise, and the resulting solution stirred at −25 °C for 3 h, warmed to 25 °C over 1 h, and stirred for a further 3 h. The reaction was quenched with aqueous NH_4Cl and subjected to a normal ether work up. Preparative g.c. used a 20% SE-30 column at 200 °C. *CAUTION*! Neat dimethylzinc is highly pyrophoric.

‡ The ratio of (**4**) : (**5**) was very sensitive to the reaction conditions.

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