METHYLENATION OF CARBONYL COMPOUNDS WITH Zn-CH2Br2-TiCl4. APPLICATIONS TO GIBBERELLINS

Luciano Lombardo

Research School of Chemistry, Australian National University P.O. Box 4, Canberra, A.C.T. 2600, Australia.

A highly active species prepared from Zn-CH2Br2-TiCl4 reacted Summary: instantaneously with aldehydes and ketones to give methylenated products with exceptional selectivity.

Methylenation of carbonyl derivatives to give olefins, i.e. $R_2C=O \rightarrow R_2C=CH_2$, by means of the Wittig reaction¹ is one of the most useful of synthetic processes. The base properties of the ylide, however, may lead *inter alia*, to epimerisation² of adjacent chiral centres or to undesired reactions with base-sensitive functionality elsewhere in the substrate. Such difficulties were experienced at several stages in our recent total syntheses of C_{19} gibberellins³ and in current attempts to extend the scope of those studies to include the preparation of C_{20} gibberellins (e.g. GA_{38}).



In particular, it was found that, during attempts to achieve a one carbon homologation of ketone 1 with ylides $Ph_3P=CH_2$ or $(CH_3)_2S=CH_2$, the respective major products (80-90%) were derived from the 8a-lpha epimer despite the fact that the latter reagent is reported 5 not to enolize ketones. Although procedures have been developed to overcome this problem, these methods are often cumbersome and low yielding, and in this case are proscribed by the presence of the ester and the ketal functions. In a search for a more effective reagent it was expected that the highly electrophilic reagent Zn/CH₂Br₂/TiCl₄ developed by Oshima $et \ a l^7$ would suppress the tendency for the ketone to enolize, but application of the procedure to substrate 1 resulted in its total destruction. However,

the desired product $\underline{2}$ was obtained in 90% isolated yield with no evidence of epimerisation⁸ when a more active reagent was prepared according to the following procedure. To a stirred suspension of zinc dust (5.75g) in CH_2Br_2 (2.02ml) and tetrahydrofuran (50ml) at -40°C was added dropwise TiCl₄ (2.3ml) over 10 min. The mixture was allowed to warm to 5°C and stirred at this temperature for 3 days to give a thick grey slurry of an active species. The active species reacted with water giving a rapid effervescence and reacted instantaneously with aldehydes and ketones to give the methylenated product. The reagent could be stored in the cold until required.



<u>3</u>



<u>5</u> a) $R = CH_3$, $R^1 = H$ b) R = H, $R^1 = H$ c) $R = CH_3$, $R^1 = OH$

CH₃ (CH₂) 10CHO

7



4

CO2CH3

CHa

<u>6</u> a) $R = CH_3$, $R^1 = H$, Y = Hb) $R = R^1 = H$, Y = Hc) $R = CH_3$, $R^{1} = OH$, Y = Hd) $R = CH_3$, $R^1 = H$, Y = De) $R = R^1 = H$, Y = D

In a typical experiment the ice-cold slurry was added portionwise to a stirred solution of the ketone in dichloromethane at room temperature until a t.l.c. monitor indicated complete reaction. The reaction mixture was poured into sodium bicarbonate:water (2:1) and ether. The mixture was shaken until a clear organic solution was obtained. For carboxylic acid substrates the reaction mixture was poured into dilute hydrochloric acid followed by extraction into bicarbonate and liberation.

In a further test of the utility of the new reagent, the nor-gibberellin ketone $\underline{3}$ was also treated. These bridged ketones are characteristically³ very prone to enolization and Wittig methylenation does not proceed to completion unless a protic solvent is employed. In the present case, however, the desired olefin $\underline{4}$ was obtained in 94% yield.

For the Wittig methylenation of other nor-gibberellin ketones, e.g 5, it had been found essential to protect³ the 3-hydroxy function so as to avoid epimerisation at C_3 . With the application of the present methodology this was not necessary, and both <u>5a</u> and its parent acid <u>5b</u> were converted into the parent gibberellins GA₄ methylester <u>6a</u>, and GA₄ <u>6b</u>, respectively in 93% and 80% isolated yield. Similarly, base catalysed acyloin rearrangement³ of the oxo-cyclopentanol system in the nor-gibberellin A₁ ketone <u>5c</u> is especially facile, but again no isomerisation was evident, and <u>6c</u> was obtained in 38% isolated yield. The reduced yield appears to have been due to complexation of the reagent with the 13-hydroxy function, thereby introducing considerable steric hindrance. Most of the substrate which had not reacted could be recovered and recycled, however.

$$R_1 - C - CH_2 - R_2 \rightarrow R_1 - C - CH_2 - R_2$$

Another much studied problem has been that involving methylenation of a carbonyl compound to obtain position specific deuterium incorporation. The existing methods^{9,6a,6c} are limited by their cumbersome nature, loss of label, scrambling, or the presence of other functionality in the molecule. In gibberellin chemistry, specific labelling¹⁰ with deuterium can be used in conjunction with mass spectrometry for identification purposes. It is known that the equivalent introduction of tritium at position 17 by carbonyl methyl-enation¹¹ of the norketone using the Wittig reaction results in significant scrambling between the 15 and 17 positions.

When the active species was generated using Zn/CD_2Br_2 (99%)/TiCl₄ and added to the ketones <u>5b</u> and <u>5a</u>, however, the deuterated analogues $17-d_2$ -GA₄<u>6e</u> and methyl ester <u>6d</u> were obtained with completely specific incorporation of deuterium to position 17.

In a final test of the methodology, aldehyde <u>7</u> was treated at 0°C; but although an improved yield (74%) of olefin was obtained relative to the Oshima procedure⁷, it was not possible to suppress completely the pinacol formation which tends to occur with aldehydes

The structure of the active species is not known but can be assumed to be a gemdimetallic⁷ species similar to $Cp_2TiCH_2AlCl(CH_3)_2^{12}$ which has considerable potential¹³ in organic synthesis. The high yields, chemoselectivity and the tolerance to other functionality in the substrate, establish the general applicability of the present procedure. It becomes the method of choice when it is necessary to maintain the stereochemical integrity of base-sensitive substrates.

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- Proof of the <u>cis</u>-ring junction of <u>2</u> was obtained by ozonolysis of <u>2</u> to yield the starting ketone <u>1</u>. Analyses and spectral data were consistent with the structures of all new compounds.
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