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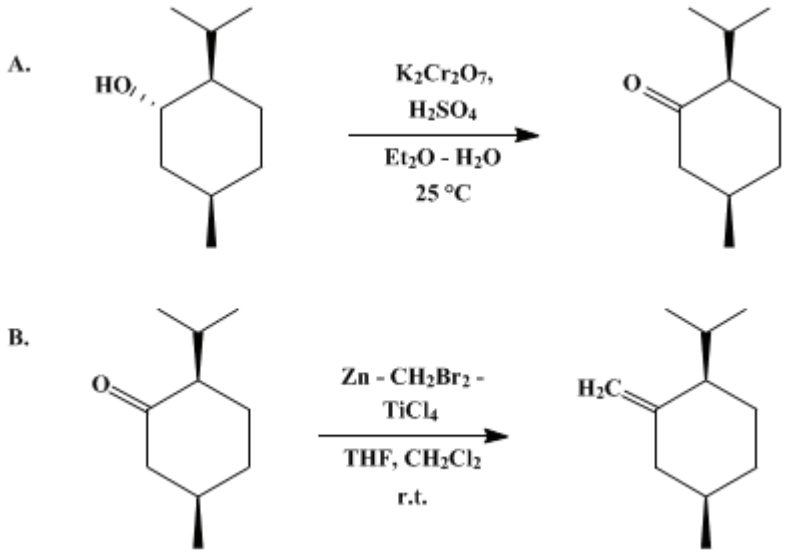
METHYLENATION OF CARBONYL COMPOUNDS: (+)-3-METHYLENE-*cis*-*p*-METHANE

[Cyclohexane, 4-methyl-2-methylene-1-(1-methylethyl)-, *R*,*R*-]



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1. Procedure

A. *(+)-Isomenthone*. Into a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel are placed 54.6 g (0.35 mol) of (+)-isomenthol (Note 1) and 350 mL of ether. A solution of chromic acid, prepared by mixing 56.7 g (0.23 mol) of potassium dichromate and 31.0 mL (0.58 mol) of 98% sulfuric acid and diluting to 200 mL with water, is added dropwise to maintain the reaction temperature at 25°C. The mixture is stirred for a further 2 hr. The ether layer is separated and the aqueous phase is extracted twice with 100-mL portions of ether. The combined ether extracts are washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure to leave an oil. Distillation through a short Vigreux column gives the main fraction of (+)-isomenthone as a clear, colorless liquid (40.5 g), bp 64–64.5°C at 5 min; $[\alpha]_D^{16}$ +114° [$CHCl_3$, *c* 5.09].

B. *(+)-3-Methylene-cis-p-menthane*. Into a 1-L, round-bottomed flask fitted with a magnetic stirrer and a pressure-equalizing dropping funnel connected to a nitrogen line are placed 28.75 g (0.44 mol) of activated zinc powder (Note 2), 250 mL of dry tetrahydrofuran (Note 3), and 10.1 mL (0.144 mol) of dibromomethane (Note 4). The mixture is stirred and cooled with a dry ice–acetone cooling bath at −40° C. To the stirred mixture is added dropwise 11.5 mL (0.103 mol) of titanium tetrachloride (Note 4) over 15 min. The cooling bath is removed and the mixture is stirred (Note 5) at 5°C (cold room) for 3 days under a nitrogen atmosphere. The dark-gray slurry (Note 6) is cooled with an ice–water bath and 50 mL of dry dichloromethane (Note 7) is added. To the stirred mixture is added 15.4 g (0.1 mol) of (+)-isomenthone in 50 mL of dry dichloromethane over a period of 10 min. The cooling bath is removed and the mixture is stirred at room temperature (20°C) for 1.5 hr. The mixture is diluted with 300 mL of pentane and a slurry of 150 g of sodium bicarbonate in 80 mL of water is added cautiously (Note 8) over 1 hr. The clear organic solution is poured of into a 1.5-L Erlenmeyer flask and the residue is washed 3 times with 50-mL portions of pentane. The combined organic solutions are dried over a mixture of 100 g of sodium sulfate and 20 g of sodium bicarbonate (Note 9) and filtered through a sintered-glass funnel (No. 2), and the solid desiccant is thoroughly washed with pentane. The solvent is

removed at atmospheric pressure by flash distillation through a column (40 × 2.5 cm) packed with glass helices. The liquid residue is distilled (Note 10) to give the methylenated product as a clear, colorless liquid, bp 105–107°C at 90 mm, 13.6 g, 89% yield (Note 11), n_D^{24} 1.45321, $[\alpha]_D^{23}$ +7.7 to +8.6° [$CHCl_3$, *c* 4.0].

2. Notes

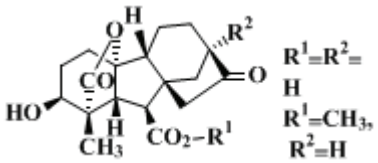
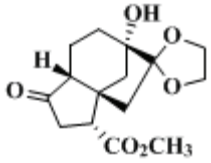
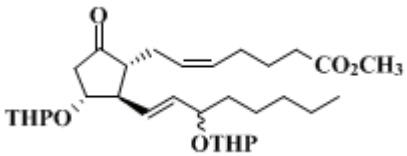
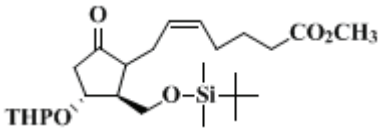
1. (+)-Isomenthol was purchased from the Aldrich Chemical Company, Inc. Oxidation was carried out according to the procedure of Brown.[2]
2. Zinc powder from Hopkin and williams Chemical Company or Nakarai Chemicals (GR grade) is activated according to Fieser and Fieser.[3]
3. Tetrahydrofuran is dried by distillation from sodium/benzophenone.
4. Dibromomethane from EGA-CHEMIE and titanium tetrachloride from E. Merck are used as supplied. The checkers used the products of Nakarai Chemicals. All residues of titanium tetrachloride are destroyed with acetone from a wash bottle.
5. As the reaction progresses the mixture thickens, and it is necessary to begin with a reasonably fast rate of stirring. However, too fast a stirring rate causes the mixture to splash up to the neck of the round-bottomed flask as the mixture thickens.
6. The reagent must be kept cold at all times because at room temperature the active reagent slowly decomposes and the mixture darkens considerably. Once prepared the reagent can be stored at −20°C (freezer) in a well-sealed flask without a significant loss of activity. A sample stored in this way for 1 year showed only a slight, ca. 5–10%, loss of activity. The molar activity of the active reagent is equivalent to the titanium tetrachloride ($TiCl_4$) molarity (determined by reaction with excess ketone followed by GLC analysis); however, an increase in the proportion of $TiCl_4$ makes no difference in the molar activity.
7. Analytical-reagent ANALAR dichloromethane was dried by storing over Linde 4A sieves. The checkers purchased the EP-grade solvent from Wako Pure Chemical Industries.
8. It is necessary to add the slurry dropwise at the beginning, allowing the effervescence to subside after each drop. After the initial vigorous effervescence, larger portions can be added. During this part of the addition, the stirrer becomes ineffective and gentle shaking by hand is continued until effervescence ceases.
9. The organic solution is shaken with the drying agent for 10–15 min to remove the last traces of titanium salts.
10. The pressure is allowed to drop to ca. 40 mm for a few minutes when the oil-bath temperature has reached 50°C. This procedure removes any residual tetrahydrofuran that could be responsible for a small contaminated forerun. A considerable amount of product is collected at the end of the distillation as the temperature drops.
11. This is the first preparation of this compound (see [4] of discussion); the data obtained are as follows. Anal. calcd. for $C_{11}H_{20}$: C, 86.83, H, 13.48. Found: C, 86.76, H, 13.24. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.79 (d, 3 H, *J* = 7, -CH_3); 0.91 (d, 6 H, *J* = 7, -CH_3); 1.01–2.14 (m, 9 H, -CH_2-, -CH); 4.54, 4.60, (two s, 2 H, =CH_2); ^{13}C NMR ($CDCl_3$): 17.4, 18.3, 19.2, 22.6, 25.8, 26.5, 31.8, 37.3, 47.4, 104.6, 148.4.

3. Discussion

This new Zn/CH_2Br_2/$TiCl_4$ procedure[5] provides a mild, nonbasic method for the methylenation of ketones (a competitive pinacol dimerization occurs with aldehydes, but good yields of the olefin can still be achieved) and offers an important alternative to the standard Wittig[6] reaction. These characteristics are derived from two important observations:

1. Ketones are not enolized by the reagent and one important consequence is that adjacent enolizable chiral centers are not epimerized.
2. The reagent is compatible with a wide variety of functional groups, for example (Table I), THP ethers, *tert*-butyldimethylsilyl ethers, acetals, esters, carboxylic acids, alcohols, and lactones. Such selectivity makes it a valuable procedure in organic synthesis[7] [8] and appreciably augments Wittig methodology.

TABLE I
METHYLENATION OF KETONES WITH
$Zn/CH_2Br_2/TiCl_4$

Substrate	Isolated Yield	Ref.
 $R^1=R^2=H$ $R^1=CH_3, R^2=H$	80% 93%	2
	90%	2
	80%	4b
	81%	4b

The corresponding Wittig reagent, $CH_2=PPh_3$, reacts smoothly with both aldehydes and ketones to give methylenated products in high yield but with one subtle limitation. The problem cannot be detected with aldehydes because they react rapidly even at temperatures as low at −78°C, but ketones react more slowly, and an adjacent enolizable chiral center can be epimerized as a result of competitive reversible enolization. This limitation of the Wittig procedure has been recognized for some time,[9] and new methylenation methods[9,10] that avoid enolization have been developed. However, the application of these methods is restricted either by low yields or by incompatibility with other functionality in the molecule. In the closest analogy to the present preparation of (+)-3-methylene-*cis*-*p*-menthane, one of these methods has been used for the methylenation of *l*-menthone,[4] but a yield of only 40% was obtained.

The $Zn/CH_2Br_2/TiCl_4$ procedure as originally reported[11] has not been widely used. The active reagent was generated and trapped by the carbonyl compound in situ at room temperature. Long reaction times were required and as a consequence the substrate was exposed for long periods to $TiCl_4$, severely limiting the usefulness of the procedure. The discovery[5] that the active reagent was stable at low temperature and could be performed extends the utility and scope of the reaction enormously. This reagent reacts rapidly with ketones at room temperature with considerably improved yields and selectivities.

The nonbasic nature of the reagent makes it useful in other applications. It has, for example, also proved useful for the methylenation of the gibberellin norketone[5] (Table I) without the need for protection of the readily epimerized 3β-OH. The use of CD_2Br_2[5] allows the introduction of $=CD_2$ without scrambling of the label.

The $Zn/CH_2Br_2/TiCl_4$ reagent is superior to other nonbasic methylenation reagents. Furthermore, the long shelf life at low temperatures, together with the ease of workup, render it an appealing alternative

to the Wittig method for the methylenation of ketones in general.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-3-METHYLENE-cis-p-METHANE

$TiCl_4$

$Zn/CH_2Br_2/TiCl_4$

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

Benzophenone (119-61-9)

zinc powder (7440-66-6)

sodium (13966-32-0)

chromic acid (7738-94-5)

Pentane (109-66-0)

potassium dichromate (7778-50-9)

(+)-isomenthol (15356-60-2)

menthone,
(+)-Isomenthone,
l-MENTHONE (1196-31-2)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

pinacol (76-09-5)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

titanium tetrachloride (7550-45-0)

(+)-3-Methylene-cis-p-menthane

cis-p-menthane

Cyclohexane, 4-methyl-2-methylene-1-(1-methylethyl)-, R,R- (122331-74-2)

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