Regioselective Methylenation and in situ Methanolation of Ketones Prone to C–C Double-Bond Isomerisation

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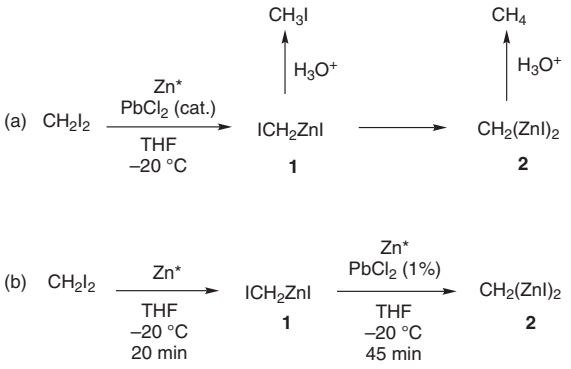
Abstract: An efficient methylenation reaction in isomer-labile ketones is described. The methylenation reaction is based on an improved method for the formation of bis(iodozincio)methane [$CH_2(ZnI)_2$]. A subsequent in situ hydroboration–oxidation sequence provides the corresponding methanol derivatives in high yields without double-bond isomerisation.

Key words: enolisable ketones, methylenation, in situ alcohol formation, titanium–zinc promotion, $CH_2(ZnI)_2$ preparation

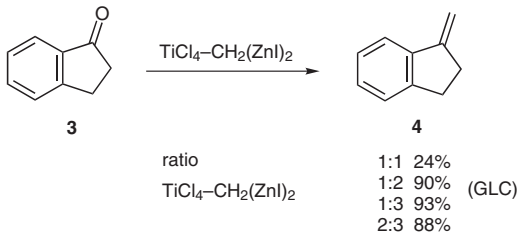
Several recent reports demonstrate the usefulness of *gem*-bis(iodozincio)methane [**2**, $CH_2(ZnI)_2$, Scheme 1] as a reagent in organic synthesis.[1–3] Typically, the reagent is prepared in a tetrahydrofuran solution in 50–60% yield from diiodomethane and acid-washed zinc dust under sonication conditions at room temperature.[3] The lead salt is believed to catalyse the transformation of the intermediate iodozinciomethyl iodide (**1**, Scheme 1) to bis(iodozincio)methane (**2**).[4] In combination with titanium(IV) chloride, this reagent provides an important alternative to Wittig reagents in the methylenation of easily enolisable ketones.[5] Double-bond migration is also a frequent problem in olefins that originate from easily enolised ketones and may complicate isolation of the methylene product that forms first.

For the preparation of active zinc reagents, Rieke 'active zinc' is generally better than acid-washed zinc.[6] In our reinvestigation of catalysed zincation of diiodomethane using Rieke zinc and lead(II) chloride, it was observed that bis(iodozincio)methane (**2**) was readily formed at low temperature, at –20 °C. The reaction was monitored by GLC after it had been quenched with one molar hydrochloric acid; toluene was used as internal standard. From iodozinciomethyl iodide (**1**), the product was iodomethane. From bis(iodozincio)methane (**2**), the product was methane (Scheme 1). By this technique it was found that formation of the desired bis(iodozincio)methane (**2**) product was incomplete after two to three hours, but that all the diiodomethane had been consumed. The second component in the mixture was the intermediate iodomethylzinc iodide (**1**), about 30%.

More iodomethylzinc iodide (**1**) accumulated when larger amounts of lead(II) chloride were added at the start of the experiment. This may mean that reduction of lead(II) chloride on the zinc surface results in partial inactivation of the metal prior to the addition of diiodomethane. This problem was avoided by addition of the lead catalyst after the addition of methylene diiodide, as shown in Scheme 1 (reaction b). Thus, the fast transmetalation with iodomethylzinc iodide (**1**) will suppress the undesired redox reaction. When this procedure was followed, GLC analysis after the acid quench indicated an effectiveness of >95% in the formation of bis(iodozincio)methane (**2**).



Scheme 1 Bis(iodozincio)methane synthesis



Scheme 2 Methylenation of indan-1-one promoted by titanium(IV) chloride

In a reinvestigation of the titanium(IV) chloride mediated methylenation reaction with bis(iodozincio)methane (**2**), the stoichiometry was investigated with indan-1-one (**3**, Scheme 2) as substrate. Equimolar amounts of titanium(IV) chloride and bis(iodozincio)methane (**2**) furnished the methylenated product **4** in low yield (24%). The yield was increased to 90% when the molar ratio of the reactants was 1:2 (Ti/Zn), and to 93% with a molar ratio of 1:3. These results complement previous findings that titanium(II) chloride is the effective titanium mediator in the methylenation reaction, and that titanium(II)

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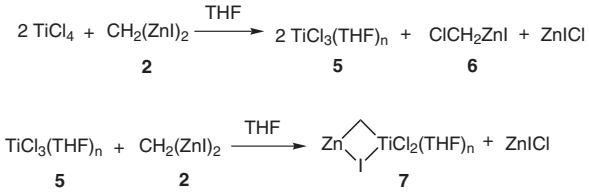
chloride initially forms by reduction of titanium(IV) chloride with bis(iodozincio)methane (**2**).[3] It has later become evident, however, that the mediator is β-titanium(III) chloride, and that methylenation is facilitated by the use of equimolar amounts of bis(iodozincio)methane (**2**) and preformed β-titanium(III) chloride.[5] Our work shows that the use of readily available titanium(IV) chloride and the easy in situ formation of the actual mediator represent an advantage for the synthetic chemist. When titanium(III) chloride is used as the mediator, the stoichiometry of the reaction should only require the use of 50% excess bis(iodozincio)methane (**2**) relative to titanium(IV) chloride and the ketone. Accordingly, when the experiment with indan-1-one (**2**) was repeated, the reactants titanium(IV) chloride and bis(iodozincio)methane (**2**) used in a molar ratio of 1:1.5 yielded olefin **4** in 88% yield.

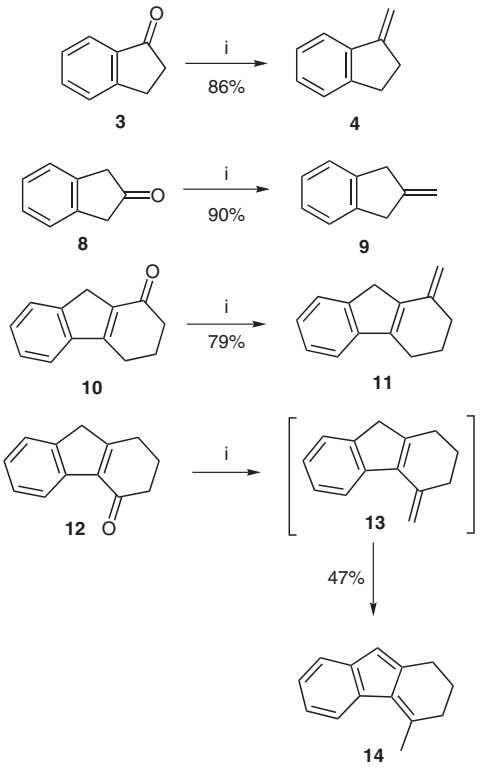
These results indicate that a reactive methylenating species **7** forms in a reaction between two molecules of titanium(IV) chloride and three molecules of bis(iodozincio)methane (**2**), as shown in Scheme 3.



Scheme 3 Postulated formation of the reactive methylene species from titanium(IV) chloride and bis(iodozincio)methane

The conditions for efficient methylenation, as described above, were subsequently applied to model reactions with easily enolisable ketones, as shown in Scheme 4. A slight excess (10%) of reactants was used. The yields of isomerically pure methylene products **4**, **9**, and **11** from the isomerically labile ketones **3**, **8**, and **10**, respectively, were high. The methylene product **13** is very easily isomerised to the methyl-substituted structure **14**, owing to extended conjugation involving the aromatic ring (Scheme 4). Attempts to isolate product **13** formed first often failed because of isomerisation to **14**.

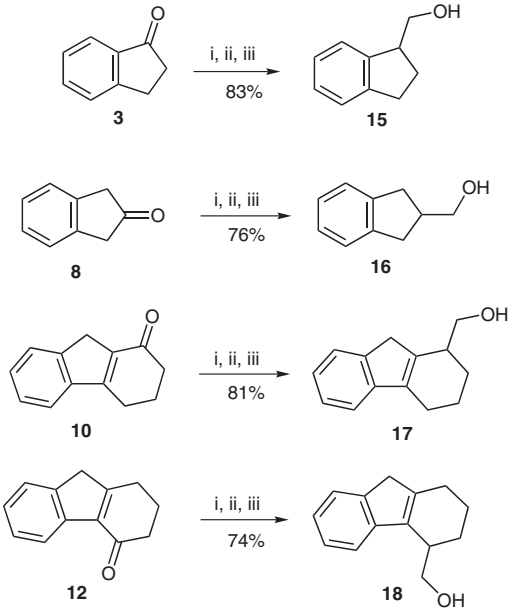
In the subsequent work, the emphasis was on developing a hydroxymethylation method without double-bond isomerisation. A tandem methylenation–hydroboration was attempted. When 9-BBN was added to the crude reaction mixture, no double-bond migration occurred. Thus, in the case of the reaction of ketone **12**, the labile olefin **13** (see Scheme 4) was trapped by a smooth in situ hydroboration reaction for which no more than 10% excess of the reagent was used (Scheme 5). Subsequent removal of iodide followed by oxidation with hydrogen peroxide provided the methanol **18** in 74% overall yield (Scheme 5). The methylenation–hydroboration reaction sequence is a practical preparative method for the reductive introduction of a functional methyl group at a carbonyl carbon where double-bond isomerisation easily occurs. The versatility of the method is further illustrated with additional examples



Scheme 4 Methylenation reactions. *Reagents and conditions*: (i) $TiCl_4$ (1.1 equiv), $CH_2(ZnI)_2$ (1.65 equiv), THF, –20 °C to 20 °C, 1 h.

(Scheme 5) in which methanol derivatives **15**, **16**, and **17**, like **18** described above, form in high yields.

The use of Rieke zinc in the preparation of bis(iodozincio)methane provides an effective method for methylena-



Scheme 5 In situ preparation of methanol derivatives by hydroxymethylation of ketones. *Reagents and conditions*: (i) $TiCl_4$ (1.1 equiv), $CH_2(ZnI)_2$ (1.65 equiv), THF, –20 °C to 20 °C, 1 h; (ii) 9-BBN (1.1 equiv), THF, 20 °C, 12 h; (iii) H_2O_2 (4 equiv), NaOH (4 equiv), THF–H_2O, 40 °C, 2 h.

tion and subsequent in situ hydroboration of easily enolisable ketones. The in situ hydroboration is particularly advantageous when the methylene compound first formed is susceptible to double-bond isomerisation.

^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded of samples in $CDCl_3$ on a Bruker DPX 200 spectrometer. Chemical shifts are reported relative to residual $CHCl_3$ (δ = 7.24) and $CDCl_3$ (δ = 77). The mass spectra were recorded at 70-eV ionising potential on a VG Prospect Sector mass spectrometer from Fissions Instruments. IR spectra were measured on a Nicolet Magma 550 spectrometer using attenuated total reflection (ATR). THF was dried by distillation from sodium–benzophenone under N_2. CH_2Cl_2 was dried by distillation from CaH_2. Anhyd $ZnCl_2$ was heated to 200 °C under 0.01 mm Hg for 20 h shortly before use. Reactions requiring dry and/or oxygen-free conditions were run under a slight positive pressure of argon gas.

Compounds 4, 9, 11, and 13 by Methylenation of Ketones; General Procedure

Li wire (0.292 g, 42 mmol) was cut in a glovebox under an argon atmosphere and placed together with naphthalene (0.538 g, 4.2 mmol) in a 100-mL round-bottomed flask. The flask was sealed with a rubber septum, THF (50 mL) was added, and the mixture was stirred at r.t. under argon for 15 min. Dry $ZnCl_2$ (3.00 g, 22 mmol) in THF (50 mL) was introduced by syringe over 3 h under vigorous stirring. The mixture was stirred for 30 min. The precipitated Rieke Zn was washed with THF and suspended in THF (50 mL), the stirred suspension was cooled to –20 °C, and CH_2I_2 (2.68 g, 10 mmol) was added over 20 min. The mixture was stirred for 30 min before neat $PbCl_2$ (97 mg, 0.20 mmol) was introduced. The cooling bath was removed after the mixture had stirred for 1 h, and then the mixture was left to stir at r.t. for 30 min. The mixture was cooled to –20 °C and $TiCl_4$ (1.27 g, 6.67 mmol) in CH_2Cl_2 (3 mL) was added dropwise before the cooling bath was removed and the mixture was left at r.t. for 45 min. The ketone (6.0 mmol) in THF (5 mL) was introduced over 5 min, and the mixture was stirred at r.t. for 1 h before hexane (50 mL) was added. The soln was washed with a sat. brine–sat. $NaHCO_3$ mixture (1:1, 30 mL), and subsequently with sat. brine (30 mL). The brine was extracted with hexane (2 × 20 mL), the combined extracts were dried ($MgSO_4$), the solvents were evaporated, and the residue was washed out with hexane; this furnished the crude alkene on evaporation of the solvents.

1-Methylene-2,3-dihydro-1*H*-indene (4)[7]

Flash chromatography (silica gel, hexane) gave compound **4**; yield: 86%.

2-Methylene-2,3-dihydro-1*H*-indene (9)[8]

Flash chromatography (silica gel, hexane) gave compound **9**; yield: 90%.

1-Methylene-2,3,4,9-tetrahydro-1*H*-fluorene (11)

The starting material 2,3,4,9-tetrahydro-1*H*-fluoren-1-one (**10**) was prepared according to a literature procedure.[9] The hexane soln of crude product **11** was subjected to rapid suction through a plug of silica gel; removal of the volatiles gave a yellow oil; yield: 0.862 g (79%). Compound **11** has limited stability because it readily undergoes double-bond migration.

IR (film): 3068 (m), 3046 (m), 3022 (m), 2921 (s), 2831 (m), 1654 (w), 1619 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.1–2.3 (m, 2 H, H-2), 2.6–2.8 (m, 4 H, H-3, H-4), 3.63 (t, *J* = 2.5 Hz, 2 H, H-9), 5.00 (s, 1 H, =C*H*H), 5.21 (s, 1 H, =CH*H*), 7.3–7.7 (m, 4 H, H-5–H-8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7 (CH_2), 23.5 (CH_2), 31.5 (CH_2), 36.2 (CH_2), 106.9 (=CH_2), 118.7 (*C*H-Ar), 123.5 (*C*H-Ar), 123.6 (*C*H-Ar), 125.1 (*C*H-Ar), 130.3, 140.3, 141.4, 141.7, 142.7.

MS (EI, 70 eV): *m*/*z* (%) = 182 (100) [M$^+$], 167 (49), 153 (24), 141 (25), 128 (27), 115 (13).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}$: 182.1095; found: 182.1093.

Compounds 15, 16, 17, and 18 by Methylenation–Hydroboration–Oxidation of Ketones; General Procedure

A 0.5 M soln of 9-BBN in THF (13.2 mL, 6.6 mmol) was added to the reaction mixture from the ketone methylenation reaction, then stirring continued for 5 min, and the turbid mixture was filtered through Celite. The filtrate was washed with an aq sat. brine–sat. $NaHCO_3$ mixture (1:1, 20 mL), and then with sat. brine until addition of H_2O_2 to some of the brine showed no formation of I_2. NaOH (2.4 g, 60 mmol) in H_2O (10 mL) and 30% H_2O_2 (6.8 g, 60 mmol) were subsequently added and the mixture was stirred vigorously at 50 °C for 2 h. Sat. aq brine (20 mL) was added and the phases were separated. The organic soln was washed with sat. aq NH_4Cl (20 mL) and sat. aq NaCl (20 mL), and then dried ($MgSO_4$) and evaporated. The residual product consisted mainly of the desired alcohol and *cis*-1,5-cyclooctadiol.

(2,3-Dihydro-1*H*-inden-1-yl)methanol (15)

Purification: flash chromatography (silica gel, hexane–EtOAc, 1:4); yield: 0.734 g (83%).

(2,3-Dihydro-1*H*-inden-2-yl)methanol (16)

Purification: flash chromatography (silica gel, hexane); yield: 0.676 g (76%)

(2,3,4,9-Tetrahydro-1*H*-fluoren-1-yl)methanol (17)

The starting material 2,3,4,9-tetrahydro-1*H*-fluoren-1-one (**10**) was prepared according to a literature procedure.[9] Purification of **17** was by flash chromatography (silica gel, hexane–EtOAc, 1:5).

White oil; yield: 0.974 g (81%).

IR (film): 3355 (s), 3065 (m), 3042 (m), 3018 (m), 2927 (s), 2859 (s), 1628 (w), 1606 (w) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.8–2.3 (m, 7 H, H-1–H-4), 2.76 (s, 1 H, OH), 3.28 (dt, *J* = 22.3, 2.7 Hz, 1 H, H-9a), 3.50 (dt, *J* = 22.3, 2.7 Hz, 1 H, H-9b), 3.74 (dd, *J* = 10.5, 6.8 Hz, 1 H, C*H*HOH), 3.82 (dd, *J* = 10.5, 5.1 Hz, 1 H, CH*H*OH), 7.2–7.5 (m, 4 H, H5–H8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7 (CH_2), 22.3 (CH_2), 26.1 (CH_2), 38.8 (C-1), 39.0 (C-9), 65.9 (COH), 117.8 (*C*H-Ar), 123.3 (*C*H-Ar), 124.0 (*C*H-Ar), 126.0 (*C*H-Ar), 138.1, 140.82, 142.8, 145.5.

MS (EI, 70 eV): *m*/*z* (%) = 200 (23) [M$^+$], 169 (100), 141 (23), 128 (15), 115 (11).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}O$: 200.1201; found: 200.1197

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.09; H, 8.15.

(2,3,4,9-Tetrahydro-1*H*-fluoren-4-yl)methanol (18)

The starting material 2,3-dihydro-1*H*-fluoren-4(9*H*)-one (**12**) was prepared according to a literature procedure.[10] Purification of **18** was by flash chromatography (silica gel, hexane–EtOAc, 1:4).

Pale yellow oil; yield: 0.884 g (74%).

IR (film): 3362 (s), 3066 (m), 3042 (m), 3018 (m), 2920 (s), 2864 (s) 1703 (w), 1626 (w), 1595 (w) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.5–2.0 (m, 7 H, H-1–H-4), 2.99 (s, 1 H, OH), 3.30 (t, *J* = 2.5 Hz, 2 H, H-9), 3.76 (dd, *J* = 10.8, 8.4

Hz, 1 H, C*H*HOH), 4.00 (dd, *J* = 10.9, 4.1 Hz, 1 H, CH*H*OH), 7.1–7.5 (m, 4 H, H-5–H-8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1 (CH_2), 25.1 (CH_2), 27.3 (CH_2), 34.6 (C-1), 40.8 (C-9), 64.1 (COH), 118.1 (*C*H-Ar), 123.5 (*C*H-Ar), 123.7 (*C*H-Ar), 126.0 (*C*H-Ar), 135.2, 142.7, 144.2, 145.2

MS (EI, 70 eV): *m*/*z* (%) = 200 (45) [M^+], 182 (35), 169 (100), 154 (13), 141 (40), 128 (18), 115 (14).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}O$: 200.1197; found: 200.1197.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found C, 83.99; H, 8.14.

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