

CHEMOSELECTIVE METHYLENATION WITH A METHYLENEDIANION SYNTHON

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Summary: The combination of $\text{CH}_2\text{I}_2\text{-Zn-Ti}(\text{O}^i\text{Pr})_4$ or $\text{CH}_2\text{I}_2\text{-Zn-Me}_3\text{Al}$ is effective for the selective methylenation of aldehydes. Selective methylenation of a ketone group is performed by pretreatment of a substrate with $\text{Ti}(\text{NEt}_2)_4$.

Chemoselectivity (referring to functional group differentiation)² presents a major challenge in organic synthesis. Organochromium³ and -titanium⁴ compounds have been found to be useful in the chemoselective carbonyl additions. We report here aldehyde⁻⁵ and ketone-selective methylenation methods using gem-dimetallated carbodanion reagent^{6,7} derived from zinc reduction of diiodomethane in the presence of Lewis acid.

Yields of the products obtained by methylenation of dodecanal and 4-dodecanone with several reagents are summarized in Table 1. The aldehyde:ketone selectivity of the Wittig reagent⁸ was not high in our hands (run 1). The methylenedianion synthon produced from CH_2Br_2 , Zn, and TiCl_4 ⁶ affords a considerable amount of the pinacol-type diol and the yield of 1-tridecene was 10% (run 2). The $\text{CH}_2\text{I}_2\text{-Zn-TiCl}_4$ system⁹ was too reactive to give selectivity (run 3). In contrast, the combination of $\text{CH}_2\text{I}_2\text{-Zn-Ti}(\text{O}^i\text{Pr})_4$ (method A) or $\text{CH}_2\text{I}_2\text{-Zn-Me}_3\text{Al}$ ⁶ was found to be highly effective for the aldehyde-selective methylenation (runs 4 and 5).^{10,11}

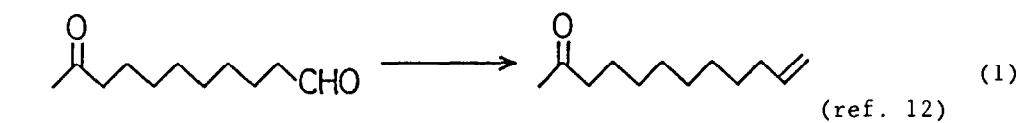
Treatment of 10-oxoundecanal with the $\text{Ti}(\text{O}^i\text{Pr})_4$ or Me_3Al system afforded exclusively 11-dodecen-2-one¹² arising from selective methylenation of the aldehyde moiety (Eq. 1). An aromatic keto aldehyde, 4-acetylbenzaldehyde, was also converted to the corresponding keto olefin in good yields with these two methods (Eq. 2).

On the other hand, selective methylenation of a ketone group was performed using the Reetz's method.¹³ The aldehyde group was protected in situ with $\text{Ti}(\text{NEt}_2)_4$ in dichloromethane. Treatment of a mixture of 4-dodecanone and the protected dodecanal with $\text{CH}_2\text{I}_2\text{-Zn-TiCl}_4$ system⁹ at 25°C

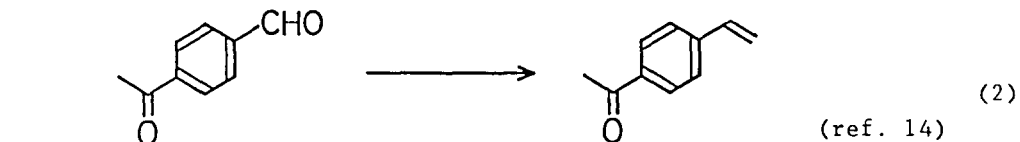
Table 1. Methylenation of a mixture of dodecanal and 4-dodecanone.^a

Run	Reagents (equiv)	Temp (°C)	Time (h)	Yields ^b (%)			
				3 (recov. 1)		4 (recov. 2)	
1	Ph ₃ P=CH ₂ (1.0)	0	0.5	12	(88)	64	(19)
2	CH ₂ Br ₂ -Zn-TiCl ₄ ^c (1.5, 4.5, 1.1)	25	2	17	(71)	10	(2) ^d
3	CH ₂ I ₂ -Zn-TiCl ₄ (5.0, 9.0, 1.0)	25	0.5	53	(25)	78	(0)
4	CH ₂ I ₂ -Zn-Ti(O ⁱ Pr) ₄ (5.0, 9.0, 1.0)	25	5	0	(97)	86	(6)
5	CH ₂ I ₂ -Zn-Me ₃ Al (3.0, 9.0, 0.6)	25	2	0	(100)	89	(6)
6	Ti(NEt ₂) ₄ , CH ₂ I ₂ -Zn-TiCl ₄ (1.1) (5.0, 9.0, 1.0)	25	0.5	95	(0)	0	(95)

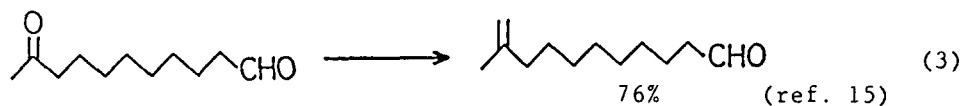
a) A mixture of dodecanal (1.0 mmol) and 4-dodecanone (1.0 mmol) was treated with a reagent in THF. b) GLPC yield (Silicone OV-17, 105°C). c) ref. 6. d) Pinacol-type dimer of dodecanal was produced as a main product (42%).



CH₂I₂-Zn-Ti(OⁱPr)₄ 25°C, 3 h 83%
 CH₂I₂-Zn-Me₃Al 25°C, 4 h 96%



CH₂I₂-Zn-Ti(OⁱPr)₄ 25°C, 2 h 80%
 CH₂I₂-Zn-Me₃Al 25°C, 1 h 86%



1. Ti(NEt₂)₄/CH₂Cl₂ 2. CH₂I₂-Zn-TiCl₄/THF, 25°C, 0.5 h 3. H₃O⁺

for 30 min gave 95% of 2-propyl-1-decene and the unchanged dodecanal (95%) after workup (Method B, run 6). Ketone-selective methylenation of 10-oxoundecanal with Method B is shown in Eq 3.

Aldehyde-selective methylenation (method A): To a stirring suspension of zinc (0.60 g, 9.0 mmol) in THF (10 ml) is added CH_2I_2 (0.40 ml, 5.0 mmol) at 25°C under an argon atmosphere. After 30 min, a THF solution of $\text{Ti}(\text{O}^i\text{Pr})_4$ (1.0 M, 1.0 mL) is added and the resulting mixture is stirred at 25°C for 30 min. A solution of 10-oxoundecanal (0.18 g, 1.0 mmol) in THF (8 mL) is then added. After being stirred for 3 h, the mixture is diluted with hexane (15 mL), poured into 1 N HCl (30 mL), and extracted with hexane (3 x 20 mL). The organic extracts are washed with brine (20 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexane-ethyl acetate, 5:1) gives 0.15 g of 11-decen-2-one¹² (83%).

Ketone-selective methylenation (method B): A solution of 10-oxoundecanal (0.18 g, 1.0 mmol) in THF (8 mL) is treated at 25°C with a CH_2Cl_2 solution of $\text{Ti}(\text{NET}_2)_4$ (1.0 M, 1.1 mL) for 30 min under an argon atmosphere.¹³ The resulting orange solution is added to a stirring suspension of the reagent⁹ prepared from CH_2I_2 (0.40 mL, 5.0 mmol), zinc (0.60 g, 9.0 mmol), and TiCl_4 (1.0 M of a CH_2Cl_2 solution, 1.0 mL) in THF (10 mL). After being stirred at 25°C for 30 min, the mixture is diluted with hexane (15 mL), poured into 1 N HCl (30 mL), and extracted with hexane (3 x 20 mL). The separated organic layer is washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. Purification of the crude product by chromatography on an alumina column (hexane-ethyl acetate, 5:1) provides 0.14 g of 10-methyl-10-undecenal¹⁵ (76%).

References and Notes

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- 10) The reagent derived from an excess amount of Zn and CH_2I_2 was reported to show a similar aldehyde selectivity.¹¹ However, addition of the Lewis acid such as Me_3Al or $\text{Ti}(\text{O}^i\text{Pr})_4$ gave better yields and reproducibility. For instance, treatment of cinnamaldehyde with the CH_2I_2 -Zn-Ti(O^iPr)₄ reagent in THF at 25°C for 45 min gave 1-phenyl-1,3-butadiene in 74% yield, while the reported yield of the same reaction without Ti(O^iPr)₄ is 29%.¹¹
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- 12) Bp 95°C (bath temp, 4 Torr); IR (neat): 3076, 2926, 2852, 1717, 1640, 1358, 993, 909 cm^{-1} ; NMR (CCl_4): δ 1.15-1.68 (m, 12H), 2.00 (s, 3H), 1.76-2.17 (m, 2H), 2.31 (t, $J=7$ Hz, 2H), 4.88 (d, $J=11$ Hz, 1H), 4.93 (d, $J=18$ Hz, 1H), 5.75 (ddt, $J=11, 18, 7$ Hz, 1H).
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- 14) Bp 99°C (bath temp, 7 Torr); IR (neat): 1679, 1604, 1402, 1357, 1267, 844 cm^{-1} ; NMR (CCl_4): δ 2.50 (s, 3H), 5.34 (d, $J=11$ Hz, 1H), 5.82 (d, $J=18$ Hz, 1H), 6.75 (dd, $J=10, 18$ Hz, 1H), 7.33-8.00 (m, 4H).
- 15) Bp 85°C (bath temp, 2 Torr); IR (neat): 3072, 2928, 2854, 2712, 1727, 1648, 1458, 885 cm^{-1} ; NMR (CCl_4): δ 1.16-1.75 (m, 12H), 1.67 (s, 3H), 1.81-2.07 (m, 2H), 2.33 (dt, $J=1, 7$ Hz, 2H), 4.63 (s, 2H), 9.75 (t, $J=1$ Hz, 1H).

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