

## $\alpha$ -Oxygen-atom Induced Methylenation of Ketones by $\text{CH}_2(\text{ZnI})_2$

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**Abstract:** Ketones bearing a hetero-atom at  $\alpha$ -position were methylenated selectively by  $\text{CH}_2(\text{ZnI})_2$  to give allylic alcohols; a nucleophilic attack of the zinc species was accelerated with a coordination of a hetero-atom at  $\alpha$ -position.

**Key words:** dimetal, methylenation, regioselective, zinc

Olefination of a carbonyl group has been an important method for organic syntheses. For this transformation, the Wittig reagent has been extensively utilized since it was devised.<sup>1</sup> This useful reaction, however, does not work in some cases owing to the lack of nucleophilicity and the relatively high basicity of the reagent. In these cases, it has been replaced with a more reactive organometallic reagent, such as the Tebbe reagent, a titanium alkylidene complex, or *gem*-dimetal compounds.<sup>2</sup> Although these olefination methods have shown the high performance in stereo- and chemoselective olefination reaction, a regioselective olefination has not been well studied except a few examples. For example, Kauffmann et al. had reported a methylenation of benzoin methyl ether in the presence of phenyl propyl ketone with a moderate selectivity.<sup>3</sup> We wish to describe the highly regioselective methylenation of ketones with or without carrying an oxygen substituent at the  $\alpha$ -position using bis(iodozincio)-methane<sup>2a</sup> ( $\text{CH}_2(\text{ZnI})_2$ , **1**). Fried et al. had also shown an  $\alpha$ -hydroxy group assisted methylenation of ketone by  $\text{CH}_2\text{I}_2$ -Zn(Cu) in ether based on an intramolecular nucleophilic attack of the reagent which reacted with hydroxy group at first.<sup>4</sup> Our method was applied not only to  $\alpha$ -hydroxy substituted ketone but also to  $\alpha$ -alkoxy, -acetoxy, and -amino substituted ketones to see the scope and limitations.

We had reported a *gem*-dizinc reagent as an effective alkylidenation reagent of ketones under mediation of titanium(II) chloride; a simple ketone did not react with the *gem*-dizinc reagent without titanium salt.<sup>2a</sup> For example, treatment of acetophenone with two molar equivalents of bis(iodozincio)-methane (**1**) in THF at 25 °C for 6 h resulted in a complete recovery of the starting material. On the contrary, treatment of  $\alpha$ -hydroxy acetophenone with two molar equivalents of **1** in THF at 25 °C for 0.5 h yielded 2-phenyl-2-propen-1-ol in 71% yield. In the reaction of  $\alpha$ -hetero-atom substituted carbonyl compounds with an organometallic reagent, the nucleophilic attack to the carbonyl group was often accelerated with coordination of the  $\alpha$ -hetero-atom.<sup>5</sup> In Table 1, the results of the methylenation of  $\alpha$ -oxygen-atom substituted ketones with **1** are summarized.<sup>6,7</sup> Hydroxy and benzyloxy groups at  $\alpha$ -posi-

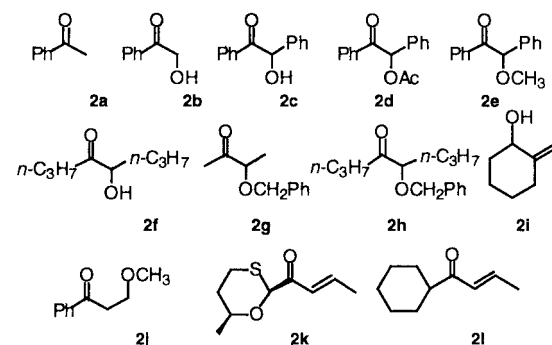
tion facilitated the reaction of  $\text{CH}_2(\text{ZnI})_2$  (**1**), while an acetoxy group did not (entry 4). A reaction of a ketone carrying an oxygen atom at the  $\beta$ -position with **1** resulted in the recovery of the starting material (entry 11). In the case of enone, a hetero-atom at the  $\alpha$ -position also induced methylenation (entry 12), thus preventing 1,4-addition (entry 13).<sup>8,9</sup>

**Table 1** Methylenation of Ketones by  $\text{CH}_2(\text{ZnI})_2$  (**1**)<sup>a</sup>

RR'C=O + CH <sub>2</sub> (ZnI) <sub>2</sub>		THF 25 °C		RR'C=CH <sub>2</sub>
	<b>2</b>	<b>1</b>		<b>3</b>
entry	<b>2</b>	<b>1</b> (eq)	3 <sup>b</sup>	Recovered <b>2</b>
1	<b>2a</b>	1.0	<5 %	>95 % <sup>c</sup>
2	<b>2b</b>	2.0	71	7
3	<b>2c</b>	2.0	79	<1
4	<b>2d</b>	1.0	3	78
5	<b>2e</b>	1.0	88	<1
6	<b>2f</b>	2.0	78	6
7	<b>2f</b>	1.0	14	76
8	<b>2g</b>	1.0	82	<1
9	<b>2h</b>	1.0	15	82
10	<b>2i</b>	2.0	90	<1
11	<b>2j</b>	2.0	6	71
12	<b>2k</b>	1.0	82	<1
13	<b>2l</b>	1.0	<1	52 <sup>d</sup>

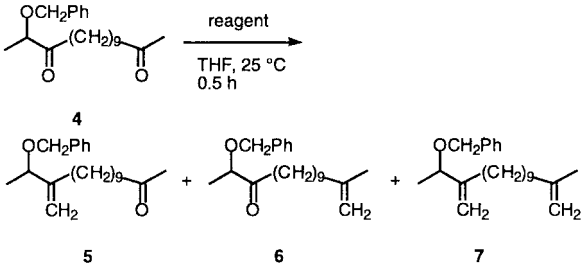
<sup>a</sup>**1** (1.0 or 2.0 mmol as indicated in Table, 0.5 M solution in THF), **2** (1.0 mmol), and THF 3 mL were mixed and stirred at 25 °C for 0.5 h.

<sup>b</sup>Isolated yields. <sup>c</sup>The reaction mixture was stirred for 6 h. <sup>d</sup>Cyclohexyl 2-methylpropyl ketone which was produced via 1,4-addition was isolated in 32% yield.



As shown in Table 2, a substrate containing two types of ketone group was treated with  $\text{CH}_2(\text{ZnI})_2$  (**1**) to examine the regioselective reaction. The  $\alpha$ -oxygen-induced methylation by **1** gave ketoalkene **5** selectively (entry 1). The titanium(II) chloride-mediated methylation<sup>2a</sup> proceeded with the reverse selectivity (entry 2). The alkoxy group at the  $\alpha$ -position might cause steric hindrance which interrupts the nucleophilic attack of the titanium mediated reagent to the carbonyl group. The Wittig reagent did not show selectivity.

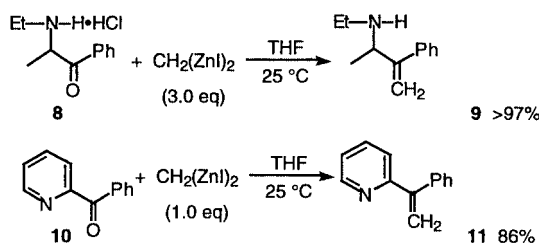
**Table 2** Regioselective Methylation of Diketone **4**<sup>a</sup>



Entry	Reagent (mmol)	<b>5</b>	<b>6</b>	<b>7</b>	<b>4</b> <sup>b</sup>
1	$\text{CH}_2(\text{ZnI})_2$ ( <b>1</b> , 2.0 mmol)	73%	<1%	<1%	25%
2	<b>1</b> (1.0 mmol) / $\text{TiCl}_2$ (1.0 mmol)	19	67	4	1
3	$\text{CH}_3\text{PPh}_3^+\text{I}^-$ / <i>n</i> -BuLi (1.0 mmol)	6	12	27	8

<sup>a</sup> The ratio of the products was obtained by <sup>1</sup>H NMR analysis. <sup>b</sup> Recovered starting material.

A nitrogen atom at  $\alpha$ -position of ketone also accelerated the reaction. As shown in Scheme 1, the transformation gave an allylic amines in good yields.



**Scheme 1**

Thus, the methylation of  $\alpha$ -hydroxy/alkoxy/amino ketone with bis(iodozincio)methane proceeded selectively even in the presence of ketone carrying no hetero-atom at  $\alpha$ -position. This method will offer a useful tool for a complex molecular transformation.

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## References and Notes

- Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
- (a) Matsubara, S.; Mizuno, T.; Otake, T.; Kobata, M.; Utimoto, K.; Takai, K. *Synlett* **1998**, 1369; Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313. (b) Knochel, P.; Normant, J.-F. *Tetrahedron Lett.* **1986**, *27*, 4427; 4431; Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241. (c) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668; Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *27*, 2417. (d) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611; Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733; Petasis, N. A.; Browej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392; Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.
- Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1258; Kauffmann, T.; Enk, M.; Fiegenbaum, P.; Hansmersmann, U.; Kaschube, W.; Papenberg, M. Toliopoulos, E.; Welke, S. *Chem. Ber.* **1994**, *127*, 127.
- Harrison I. T.; Rawson, R. J.; Turnbull, P.; Fried, J. H. *J. Org. Chem.* **1971**, *36*, 3515.
- Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778; Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.
- A reaction of 1,2-diketone with bis(iodozincio)methane (**1**) gave cyclopropane-1,2-diol; Ukai, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* **2000**, *122*, 12047.
- Study for diastereoselectivity in the reaction of  $\alpha$ -hydroxy ketone with ethylenetriphenylphosphorane; Koreeda, M.; Patel, P. D.; Brown, L. *J. Org. Chem.* **1985**, *50*, 5910; Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2629.
- Matsubara, S.; Arioka, D.; Utimoto, K. *Synlett* **1999**, 1253.
- Bis(iodozincio)methane (**1**) in THF was prepared following the reported procedure.<sup>2a</sup> To a solution of  $\alpha$ -hetero-atom substituted ketone (1.0 mmol) in THF (3.0 mL) was added **1** (0.5 M THF solution, 2.0 mmol) dropwise at 25 °C. The mixture was stirred for 0.5 h at 25 °C. The mixture was poured into 1 M HCl (15 mL) and extracted with ether. The product was isolated with a short silica gel column chromatography.

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