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Science Letters:

A novel reduction of diketones with i-RMgBr catalyzed by Cp_2TiCl_2 and deoxygenation of sulfoxides by Cp_2TiCl_2/Al system*

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Abstract: α-diketones and β-diketones react with Grignard reagents in the presence of a catalytic amount of Cp_2TiCl_2 to yield α-ketols and corresponding ketones respectively. Sulfoxides can be deoxygenated by Cp_2TiCl_2/Al system. The possible mechanisms are also discussed.

Key words: Grignard reagent, Cp_2TiCl_2-catalyzed, α-diketone, β-diketone, Reduction
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INTRODUCTION

It was reported that Grignard reagent containing β-H could reduce alkyl ketones, aldehydes and esters to their corresponding alcohol in the presence of a catalytic amount of Cp_2TiCl_2 (Sato *et al*., 1980). However, this method is not applicable to aromatic and α, β-unsaturated ketones. It was also reported that the Cp_2TiCl_2-catalyzed hydromagnesiation reaction of alkynes had recently become widely used in organic synthesis (Sato and Kobayashi, 1990; Gao and Sato, 1995; Xu and Huang, 1997). We described the Cp_2TiCl_2-catalyzed reduction of imines, isocyanates and β-diketones by Grignard reagents (Zhang and Hu, 1988; Zhang *et al*., 1987; 1988; Yu and Zhang, 1999). As an extension of this methodology, we report below our preliminary results showing the unexpected behavior of 1,2-diketones and 1,3-diketones. When the reaction of Grignard reagents with α-diketones was carried out in the presence of a catalytic amount of Cp_2TiCl_2 reduction dominated and the usual addition was suppressed (Fig.1).

Table 1 shows that under mild reduction condition α-diketones may be reduced and result in good yields; and that the significant advantage is that the products are always α-ketol even with excessive Grignard reagents and Cp_2TiCl_2. In addition, the choice of solvent plays an important role. Switching from ether to THF lowered the yield of reductive products. We also found that t-BuMgBr was more effective than i-PrMgBr in this case.

The mechanism proposed for Cp_2TiCl_2-catalyzed reduction of carbonyl compounds. We assume that the actual reducing agent of the present reaction is [Cp_2TiH] as shown in Fig.2. Sato reported that the Cp_2TiCl_2-catalyzed reduction failed with aryl aldehydes, and that aryl and α, β-unsaturated ketones may be rationalized by the π-d coordinated bond between the π-bond of the substrates and the

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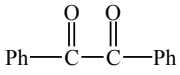
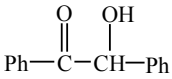
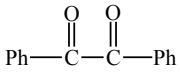
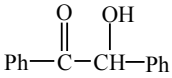
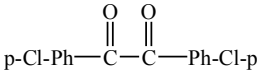
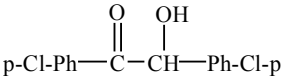
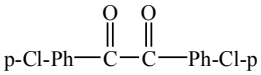
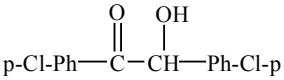
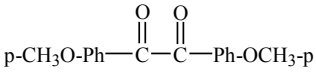
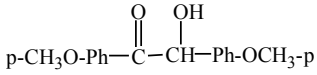
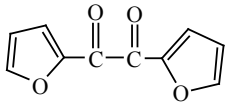
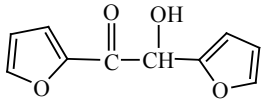
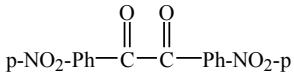
Table 1 Cp_2TiCl_2-catalyzed reduction of α-diketones by RMgBr

Entry	α-diketone	RMgBr	Product	Yield (%)[a]
2a		i-PrMgBr		83
2a		i-BuMgBr		96
2b		i-PrMgBr		76
2b		i-BuMgBr		95
2c		i-PrMgBr		24
2d		i-PrMgBr		71
2e		i-PrMgBr	– [b]	0

[a]: Isolated yields based on α-diketones; [b]: In such case, product 2 was not isolated

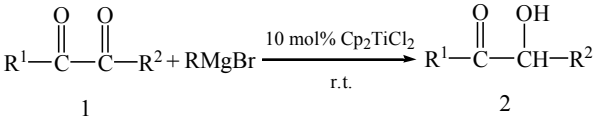


Fig.1 Reduction of α-diketones by RMgBr

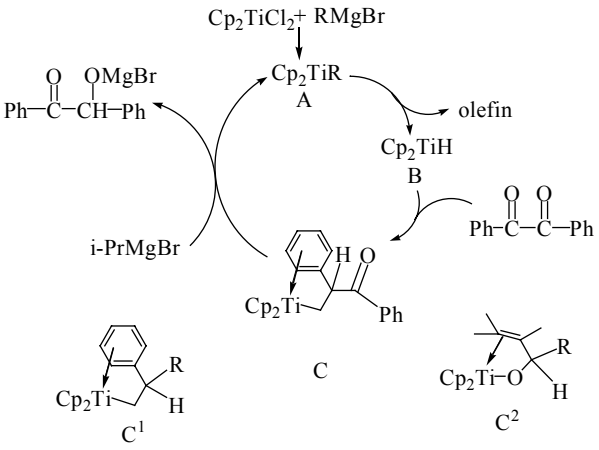


Fig.2 The possible mechanism of reduction of α-diketones

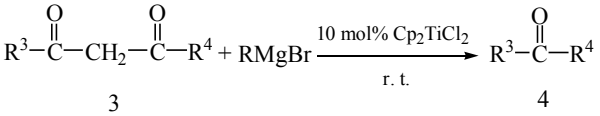
titanium atom as shown in C^1 and C^2. Apparently, the intermediate C^1 and C^2 can be stabilized by this π-d bond, and the required reducing agent [Cp_2TiH] in the Cp_2TiCl_2-catalyzed reaction cycle may not be reproduced. Thus the favorable 1,2-addition of Grignard reagent gave rise to the tertiary alcohol. When substrates bearing α-electron-withdrawing carbonyl make the intermediate C fairly reactive and easily exchange with Grignard reagent, the [Cp_2TiH] can be reproduced promptly during the reaction process. Therefore, as the catalytic cycle goes on, reduction becomes the major pathway. However, when one carbonyl group has been reduced, the α-hydroxy group formed, cannot make the intermediate reactive enough to exchange with the Grignard reagent, so the catalytic cycle may be stopped and the products are only α-ketols.

We found that when α, β-diketones react with Grignard reagent in the presence of a catalytic amount of Cp_2TiCl_2, the C-C bond of β-diketones was reductively cleaved, with the products being the corresponding ketones, not β-ketols (Fig.3).

The results are summarized in Table 2.

By analogy with the mechanism proposed above, we suggest that the key intermediate of this catalytic C-C bond cleavage reaction is [Cp_2TiH]. A possible mechanism may be described as shown in Fig.4: [Cp_2TiH] reacted with β-diketones to form intermediate C^3 which is fairly reactive and easily exchanges with Grignard reagent, while the C-C bond of the intermediate C^3 is cleaved.

We recently found that Cp_2TiCl_2 can be reduced by samarium to form a low-valent cyclopentadienyl titanium complex, which is a very effective reducing reagent (Yu and Zhang, 1995; Nugent and Rajanbabu, 1988). In order to extend the scope of application of the low-valent cyclopentadienyl titanium complex, we report that the Cp_2TiCl_2/Al system can be used as a deoxygenation reagent for reducing sulfoxides to sulfides under neutral and mild conditions (Fig.5).



3 4

Fig.3 Reduction of β-diketones by RMgBr

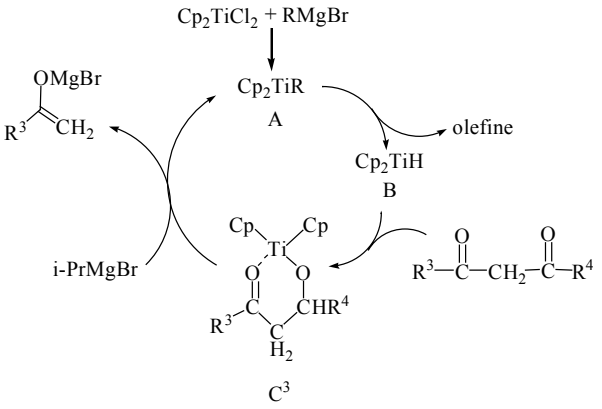
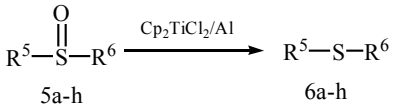


Fig.4 The possible mechanism of reduction of β-diketones



5a-h 6a-h

a: R^5=Ph; R^6=Me b: R^5=Ph; R^6=Et

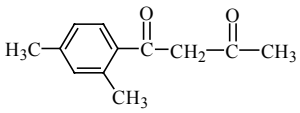
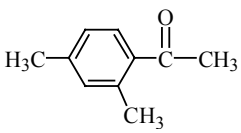
c: R^5=Ph; R^6=n-Pr d: R^5=Ph; R^6=i-Pr

e: R^5=Ph; R^6=n-Bu f: R^5, R^6=p-$CH_3C_6H_4$

g: R^5=Ph; R^6=Ph h: R^5, R^6=p-ClC_6H_4

Fig.5 Reduction of sulfoxides by Cp_2TiCl_2/Al system

Table 2 Cp_2TiCl_2-catalyzed reduction of β-diketones by RMgBr

Entry	β-diketone	Product	Yield (%)[a]
4a	Ph—C(=O)—CH_2—C(=O)—CH_3	Ph—C(=O)—CH_3	63
4b	p-Cl-Ph—C(=O)—CH_2—C(=O)—CH_3	p-Cl-Ph—C(=O)—CH_3	68
4c	p-Br-Ph—C(=O)—CH_2—C(=O)—CH_3	p-Br-Ph—C(=O)—CH_3	31
4d	p-CH_3-Ph—C(=O)—CH_2—C(=O)—CH_3	p-CH_3-Ph—C(=O)—CH_3	60
4e			58
4f	Ph—C(=O)—CH_2—C(=O)—Ph	—[b]	0

[a]: Isolated yields based on β-diketones; [b]: In such case, product 4 was not isolated

When sulfoxide is added to the THF solution from the reduction of Cp_2TiCl_2 by Al, the reaction mixture becomes red immediately and the red solid is precipitated. In this reaction, the S–O bond in sulfoxide is cleaved and the oxygen atom is transferred to Cp_2TiCl_2 to generate the stable +4 valent titanium complex, accompanied by the formation of sulfide. Compared with the Cp_2TiCl_2/i-PrMgBr system, the Cp_2TiCl_2/Al system reduces sulfoxides more smoothly and the yields are much higher. This may due to avoidance of sulfonium salt formation arising from the side reaction of i-PrMgBr with sulfoxide.

EXPERIMENT DETAILS

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AC-80 spectrometer using TMS as an internal standard. Chemical shifts (δ) were reported in ppm. IR spectra were taken as thin films with a Bruker Vector-22 infrared spectrometer. The reaction was achieved in a Schlenk type glass apparatus and nitrogen atmosphere.

General procedure for Cp_2TiCl_2-catalyzed reduction of α-diketones (or β-diketones)

The reaction was performed under nitrogen atmosphere. Isopropylmagnesium bromide in ether (20 ml, 1.0 mol/L) was added to an ether solution of Cp_2TiCl_2 (0.25 g, 1 mmol), and the mixture was stirred for 10 minutes at room temperature. Then α-diketones or β-diketones (10 mmol) in dry ether (10 ml) were slowly added dropwise under nitrogen within about 1 h. The resulting mixture was stirred for 4 h at 35 °C. The reaction mixture was then acidified with HCl (25 ml, 2 mol/L), and extracted with ether (20 ml ×3). The combined ether was dried over anhydrous magnesium sulfate. The solvent was evaporated and the crude product was recrystallized from alcohol or purified by distillation. The products were fully characterized as shown by their ^{1}H NMR and IR spectra, and m.p. data.

Compound 2a: m.p. 132 °C–134 °C. ^{1}H NMR ($CDCl_3$) 4.0 (1 H, s), 5.84 (1 H, s), 7.35–8.0 (10 H, m). IR (KBr) 3400, 1680, 1467, 848.

Compound 2b: m.p. 87 °C–88 °C. ^{1}H NMR ($CDCl_3$) 3.5 (1 H, s), 6.0 (1 H, s), 7.30–8.20 (8 H, m). IR (KBr) 3400, 1675, 1468, 845.

Compound 2c: m.p. 112 °C–113 °C. ^{1}H NMR ($CDCl_3$) 3.6 (6 H, s), 4.1 (1 H, s), 5.9 (1 H, s), 6.90–7.80 (8 H, m). IR (KBr) 3450, 1680, 1460, 845.

Compound 2d: m.p. 137 °C–138 °C. ^{1}H NMR ($CDCl_3$) 5.0 (1 H, s), 5.80 (1 H, s), 6.50–7.90 (6 H, m). IR (KBr) 3350, 1685, 1460, 845.

Compound 4a: b.p. 117 °C–120 °C/20 mmHg. ^{1}H NMR ($CDCl_3$) 2.45 (3 H, s), 7.20–7.87 (5 H, m). IR (KBr) 1690, 1455, 670.

Compound 4b: b.p. 114 °C–116 °C/14 mmHg. ^{1}H NMR ($CDCl_3$) 2.55 (3 H, s), 7.32–7.91 (4 H, m). IR (KBr) 1685, 1458, 675.

Compound 4c: b.p. 128 °C–130 °C/15 mmHg. ^{1}H NMR ($CDCl_3$) 2.55 (3 H, s), 7.28–7.86 (4 H, m). IR (KBr) 1680, 1460, 675.

Compound 4d: b.p. 108 °C–110 °C/10 mmHg. ^{1}H NMR ($CDCl_3$) 2.31 (3 H, s), 2.52 (3 H, s), 7.16–7.89 (4 H, m). IR (KBr) 1685, 1450, 675.

Compound 4e: b.p. 120 °C–121 °C/10 mmHg. ^{1}H NMR ($CDCl_3$) 2.30 (3 H, s), 2.50 (6 H, s), 7.54–7.65 (4 H, m). IR (KBr) 1680, 1455, 675.

General procedure for reduction of sulfoxides by Cp_2TiCl_2/Al

Cp_2TiCl_2 (1 g, 4 mmol), aluminium power (0.13 g, 5 mmol) and THF (15 ml) were mixed under nitrogen atmosphere and the resulting mixture was stirred at room temperature for 1.5 h. A blue solution was obtained. Sulfoxide (2 mmol) was added to the solution. The reaction mixture was stirred for 2 h at room temperature under nitrogen. After the solvent was evaporated under reduced pressure, the residue was diluted with 30 ml petroleum ether and filtered. The filtrate was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether:ether=10:1 as eluent).

Compound 6a: b.p. 61 °C–62 °C/5 mmHg. ^{1}H NMR ($CDCl_3$) 2.50 (3 H, s), 7.29 (5 H, m). IR: 3080, 1870, 1450, 1095.

Compound 6b: b.p. 50 °C–52 °C/4 mmHg. ^{1}H NMR ($CDCl_3$) 1.30 (3 H, t), 2.95 (2 H, q), 7.30 (5 H, m). IR: 3080, 2990, 1448, 1060.

Compound 6c: b.p. 72 °C–73 °C/4 mmHg. ^{1}H NMR ($CDCl_3$) 1.05 (3 H, t), 2.70 (2 H, m), 2.93 (2 H, t), 7.30 (5 H, m). IR: 3080, 2970, 1445, 1095.

Compound 6d: b.p. 70 °C–72 °C/4 mmHg. ^{1}H NMR ($CDCl_3$) 1.30 (6 H, d), 3.40 (1 H, m), 7.35 (5 H, m). IR: 3080, 2980, 1448, 1060.

Compound 6e: b.p. 90 °C–95 °C/4mmHg. ^{1}H NMR ($CDCl_3$) 0.92 (3 H, t), 1.60 (4 H, m), 2.92 (2 H, t), 7.30 (5 H, m). IR: 3080, 2990, 1448, 1060.

Compound 6f: m.p. 55 °C–56 °C. ^{1}H NMR ($CDCl_3$) 2.32 (6 H, m), 7.18 (8 H, m). IR: 3040, 1550, 820.

Compound 6g: b.p. 88 °C–90 °C/1 mmHg. ^{1}H NMR ($CDCl_3$) 7.36 (10 H, m). IR: 3080, 1890, 1448, 1060.

Compound 6h: m.p. 94 °C–95 °C ^{1}H. NMR ($CDCl_3$) 7.25 (8 H, s). IR: 3090, 1095, 810.

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