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A Novel Cyclodimerization of α , β -Unsaturated Ketones Induced by Low-valent Titanium

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Abstract: The intermolecular and intramolecular coupling reaction of α , β -unsaturated ketones induced by $TiCl_4$-Zn was studied. A possible reaction mechanism was proposed.
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We recently reported that the low-valent titanium reagent induced intermolecular reductive coupling reactions of nitro compounds with nitriles[1], carbonyl compounds with nitriles[2] and intramolecular or intermolecular coupling reactions of carboxylic derivatives with ketones[3]. Although several results are reported on saturated ketones, only few studies concerning unsaturated ketones have been published. Pons reported that the reduction of mesityl oxide with low-valent titanium only gave intermolecular coupling products 2,4,5,7-tetramethyl-octa-2,4,6-triene and 2,4,5,7-tetramethyl-octa-2,6-dien-4,5-diol[4]. We now describe our preliminary results on a novel cyclodimerization via an intermolecular reductive cross coupling of α , β -unsaturated ketones by $TiCl_4$-Zn, which differ from saturated ketones and mesityl oxide, to yield substituted cyclopentanols.

When α , β -unsaturated ketones **(1)** were treated with low-valent titanium, the cyclodimerization products 2-aroyl-1,3,4-triaryl cyclopentanol derivatives **(2)** were obtained along with their stereoisomers 2-aroyl-1,3,4-triaryl cyclopentanol **(3)**[5].

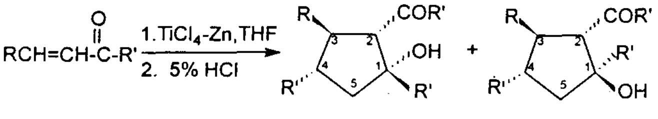
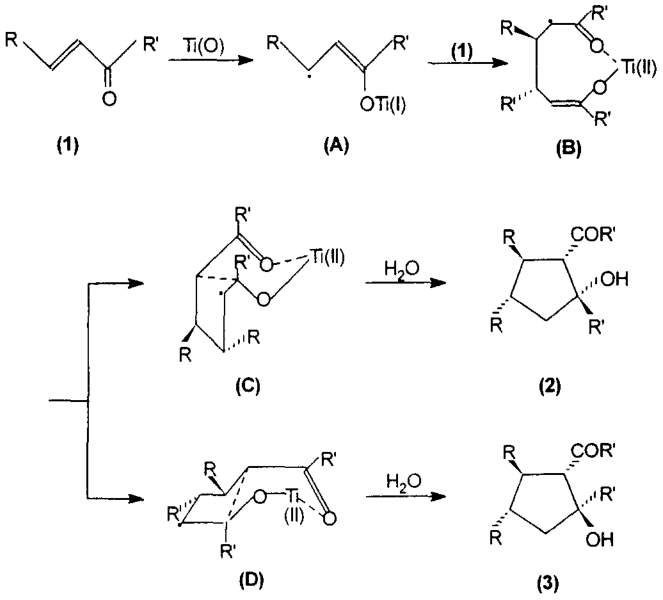


Table 1. TiCl$_4$-Zn induced cyclodimerization of α, β -unsaturated ketones

		Isolated	Yield (%)
R	R'	2	3
Ph	Ph	43.2	23.9
Ph	4-CH$_3$C$_6$H$_4$	51.8	15.8
Ph	4-CH$_3$OC$_6$H$_4$	59.1	9.1
4-ClC$_6$H$_4$	Ph	41.1	16.5
4-CH$_3$C$_6$H$_4$	Ph	47.3	20.3
3,4-OCH$_2$OC$_6$H$_3$	Ph	39.7	15.9
3,4-OCH$_2$OC$_6$H$_3$	4-CH$_3$C$_6$H$_4$	59.5	11.2
3,4-OCH$_2$OC$_6$H$_3$	4-CH$_3$OC$_6$H$_4$	63.8	

The reaction is in striking contrast with that in the case of SmI$_2$ and YbI$_2$[6] and CeCl$_3$/NaBH$_4$[7] and not in agreement with that in literature[5]. The mechanism of this reaction may be postulated as scheme I.

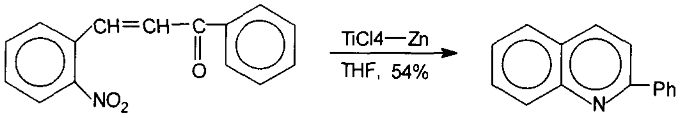


Scheme I

$TiCl_4$ is reduced by Zn dust to give low-valent titanium. In the initial step, an electron is transferred from low-valent titanium to chalcone **(1)** to give radical enolate **(A)**, the radical anion then attacks the chalcone to form the carbon-carbon bond and generates intermediate **(B)**. The latter then would be transformed to **(2)** and **(3)** through a stable chair form transition state **(C)** and a less stable boat form **(D)**, respectively.

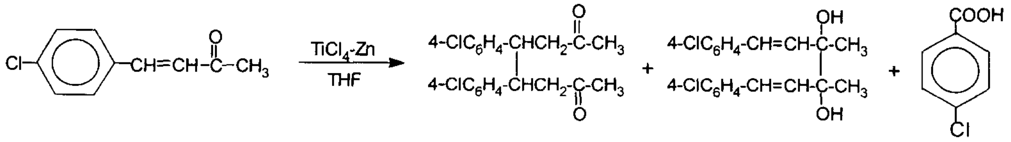
A general experimental procedure is as follows: A dry 100ml flask was charged with zinc dust (2.60g, 40mmol), $TiCl_4$(2.2ml, 20mmol) and THF(20ml). The mixture was refluxed for 2h under argon atmosphere, then cooled to room temperature. A black slurry was formed. A solution of chalcone (10mmol) in the THF(15ml) was dropped to the reaction mixture in five minutes. After being stirred for 0.5h at r.t., the mixture was quenched with 5%HCl (50ml) and extracted with $CHCl_3$ (3 × 30ml). The combined organic layer was washed with water (2 × 30ml), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate : benzene : petroleum ether (60-90 ℃), 1 : 4 : 8) to give **(2)** and **(3)** [8].

However, treatment of 2-nitrochalcone **(4)** with $TiCl_4$-Zn in the THF under the same reaction condition only afforded 2-phenylquinoline **(5)**[9], which is the intramolecular reductive cyclization product. The cyclodimerization products **(2 and 3)** of chalcone were not obtained.



(4) **(5)**

On the other hand, the reaction of α , β -unsaturated ketone **(6)** with the same reagent afforded 4,5-di(4'-chlorophenyl)-octa-2,7-dione**(7)** (22.4%) and 1,6-di(4'-chlorophenyl)-3,4-dimethyl-hexa-1,5-dien-3,4-diol **(8)** (18.6%) along with 4-chlorobenzoic acid **(9)** (28.5%)[10]. The formation of **(9)** is interesting, since the reduction does not take place formally as with **(1)** and **(4)** and other ketones, however the mechanism is uncertain at present.



(6) **(7)** **(8)** **(9)**

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8. Selected data for compounds (2) and (3): 2a, mp 192-194 °C. IR(KBr, ν, cm^{-1}): 3440(OH), 1640(CO).^{1}HNMR(500MHz,CDCl$_3$, δ ppm):7.10-7.57(20H, m, ArH), 5.20(1H,s,OH,exchangeable), 4.53(1H, d, J 11.7Hz, C^{2}H), 4.10(1H, dd, J 11.7, 10.2Hz, C^{3}H), 3.76(1H, ddd, J 10.7, 10.2, 6.1Hz, C^{4}H), 3.00(1H, dd, J 14.4, 10.7Hz, C^{5}H), 2.58(1H, dd, J 14.4, 6.1Hz, C^{5}H). Elemental analysis: found(%): C, 86.17; H, 6.20; Calc. For $C_{30}H_{26}O_2$: C, 86.09; H, 6.26.

   3a, mp 229-231 °C. IR(KBr, ν, cm^{-1}): 3500(OH), 1660(CO). ^{1}HNMR(500MHz,CDCl$_3$, δ ppm): 7.07-7.48(20H, m, ArH), 4.51(1H, d, J 5.4Hz, C^{2}H), 3.94-3.99(2H, m, C^{3}H, C^{4}H), 3.15(1H, dd, J 12.7, 6.3Hz, C^{5}H), 2.37(1H, dd, J 12.7, 5.0Hz, C^{5}H),2.05(1H,s,OH,exchangeable). Elemental analysis: found(%): C, 86.23; H, 6.37; Calc. For $C_{30}H_{26}O_2$: C, 86.09; H, 6.26.
9. Using 10% aqueous K_2CO_3 to quench the reaction mixture and using eluent (dichloromethane : petroleum ether(60-90 °C), 1:1) to purify the product are difference from the general procedure.
10. Using eluent (ethyl acetate: petroleum ether(60-90 °C),1:4) to isolate the reaction mixture is only difference from the general procedure.

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