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# Low–valent Titanium Induced Reductive Coupling Reaction of Carboxylic Derivatives with Aromatic Ketones

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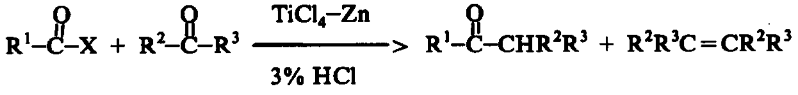
Abstract: The intermolecular and intramolecular coupling reaction of carboxylic derivaties with aromatic ketones induced by titanium tetrachloride and zinc powder was studied.

We recently reported that the low–valent titanium reagent induced intermolecular reductive coupling reactions of nitro compounds with nitriles[1] and carbonyl compounds with nitriles[2]. We now describe the coupling reaction of carboxylic derivatives with aromatic ketones by treatment with titanium tetrachloride and zinc in tetrahydrofuran at refluxing temperature.

When an acyl chloride (1) and aromatic ketone (2) were treated with $TiCl_4$–Zn , the cross coupling product ketone (3) was obtained along with an olefin(4) the self–reductive coupling product of ketones . The self–reductive coupling product of carboxylic derivatives was not obtained. The same outcome was also found in the cross coupling of aromatic ketone with an ester. Aliphatic ketones failed to give similar ketone products under the same conditions.



$$\underset{\textbf{1}}{R^1\text{–}\overset{O}{\overset{\|}{C}}\text{–}X} + \underset{\textbf{2}}{R^2\text{–}\overset{O}{\overset{\|}{C}}\text{–}R^3} \xrightarrow[3\%\ HCl]{TiCl_4\text{–}Zn} \underset{\textbf{3}}{R^1\text{–}\overset{O}{\overset{\|}{C}}\text{–}CHR^2R^3} + \underset{\textbf{4}}{R^2R^3C{=}CR^2R^3}$$

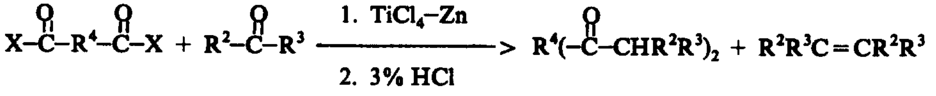
Table: $TiCl_4$ / Zn induced reductive coupling of ketones with acyl chlorides or esters.

| <u>1</u> | | <u>2</u> | | Isolated Yield(%) | |
|---|---|---|---|---|---|
| X | $R^1$ | $R^2$ | $R^3$ | <u>3</u> | <u>4</u> |
| Cl | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 68.6 | 24.1 |
| Cl | 4–$ClC_6H_4$ | $C_6H_5$ | $C_6H_5$ | 52.2 | 27.1 |
| Cl | 3–$ClC_6H_4$ | $C_6H_5$ | $C_6H_5$ | 47.8 | 21.1 |
| Cl | 3–$CH_3C_6H_4$ | $C_6H_5$ | $C_6H_5$ | 60.6 | 18.1 |
| Cl | 4–$CH_3OC_6H_4$ | $C_6H_5$ | $C_6H_5$ | 66.7 | 30.1 |
| Cl | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 69.8 | 15.1 |
| $OC_2H_5$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 46.6 | 30.1 |
| $OC_2H_5$ | $C_6H_5CH_2$ | $C_6H_5$ | $C_6H_5$ | 49.0 | 18.1 |
| $OC_2H_5$ | 1–$C_{10}H_7CH_2$ | $C_6H_5$ | 4–$ClC_6H_4$ | 70.3 | 20.7 |
| $OC_2H_5$ | 1–$C_{10}H_7CH_2$ | $C_6H_5$ | $C_6H_5$ | 66.7 | 24.0 |
| $OC_2H_5$ | 1–$C_{10}H_7CH_2$ | $C_6H_5$ | 4–$CH_3C_6H_4$ | 48.6 | 29.6 |
| $OC_2H_5$ | 1–$C_{10}H_7CH_2$ | $C_6H_5$ | 4–$CH_3OC_6H_4$ | 44.4 | 25.5 |

The mechanism of this titanium–induced intermolecular coupling reaction of carboxylic derivative with aromatic ketone appears to be an exact analogue of the keto ester cyclization[3]. In the initial step, an eletron is transferred from titanium to the carbonyl group generating a radical anion, the ketyl radical then dimerizes to yield olefin or attacks carboxylic derivative to yield the cross coupling product ketone.

However, treatment of benzophenone and formic ester under the same reaction condition afforded 1,1,3,3–tetraphenyl propylene and tetraphenyl ethylene.

We could also obtain diketone (6) from a diacyl chloride or a dicarboxylic ester and two equivalents of aromatic ketone under the same reaction conditions.

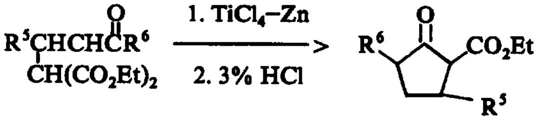


$$X-\overset{O}{\overset{\|}{C}}-R^4-\overset{O}{\overset{\|}{C}}-X + R^2-\overset{O}{\overset{\|}{C}}-R^3 \xrightarrow[2.\ 3\%\ HCl]{1.\ TiCl_4-Zn} R^4(-\overset{O}{\overset{\|}{C}}-CHR^2R^3)_2 + R^2R^3C=CR^2R^3$$

5 2 6 4

| | 5 | | 2 | Isolated Yield(%) | |
|---|---|---|---|---|---|
| X | $R^4$ | $R^2$ | $R^3$ | 6 | 4 |
| Cl | 1,4–$C_6H_4$ | $C_6H_5$ | $C_6H_5$ | 40.7 | 38.6 |
| $OC_2H_5$ | $(CH_2)_4$ | $C_6H_5$ | $C_6H_5$ | 50.5 | 28.5 |

On the other hand, the reaction of keto–diester (7) with the same reagent afforded the cyclic $\beta$–keto–ester in good yields. Compound 7 can be prepared easily from $\alpha,\beta$–unsaturated ketone and malonic ester.[4]



7 8

| 7 | | 8 |
|---|---|---|
| $R^5$ | $R^6$ | Yield(%) |
| $C_6H_5$ | $C_6H_5$ | 81 |
| $C_6H_5$ | 4–$CH_3C_6H_4$ | 87 |
| 3,4–$Cl_2C_6H_3$ | 4–$CH_3C_6H_4$ | 78 |

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