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Reductive Cross Coupling Reaction of a Glyoxylate with Carbonyl Compounds. A Facile Synthesis of α,β-Dihydroxycarboxylate Based on a Low Valent Titanium Compound

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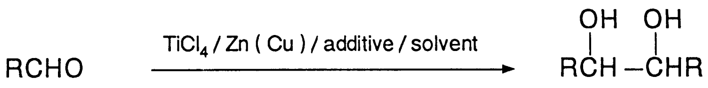
On treatment with a low valent titanium compound, a glyoxylate is reductively converted to the titanium enediolate, which reacts with carbonyl compounds to give the corresponding adducts, α,β-dihydroxycarboxylates, in good yields.

Glyoxylic acid and its ester derivatives have been used as important and versatile reagents in many types of reactions such as the Mannich,[1)] aldol,[2)] Diels-Alder,[3)] Wittig,[4)] and Prinse[5)] type reactions, etc. In the above reactions, they have been used as efficient electrophiles and, as far as we know, there have been no example that they worked as nucleophiles.

In this communication, we wish to report the cross aldol-type reaction of a glyoxylate as a nucleophilic component with carbonyl compounds yielding the corresponding diols by using a low valent titanium compound prepared from $TiCl_4$ and Zn. We have already reported the reductive self-coupling reaction of carbonyl compounds to the corresponding pinacols by making use of the reducing ability of the low valent titanium compound. Based on the above results, it was considered that the low valent titanium compound would reduce glyoxylate to form the corresponding titanium enediolate which in turn reacts with another carbonyl compound to form the cross aldol-type adduct, α,β-dihydroxycarboxylic acid ester.

First, we examined the effect of solvents on the reductive self-coupling reaction of 3-phenylpropanal. As shown in Table 1, ethers such as 1,2-dimethoxyethane (DME) and THF gave the corresponding diols in high yields. In the present attempt, the above self-coupling reaction should be suppressed because it is undesirable for the purpose of performing the cross coupling reaction between a glyoxylate and 3-phenylpropanal. Further investigation made it possible to suppress the self-coupling reaction of 3-phenylpropanal by carrying out the reaction in dichloromethane at lower temperature (-23 °C) along with an additive, 1,2-dimethoxyethane. Under the reaction condition, the preliminary reduction of glyoxylic acid benzylester proceeded smoothly because of its high reactivity.

Next, the reaction conditions for the cross coupling reaction were examined and it was found that when the mixture of benzylglyoxylate and 3-phenylpropanal (6:1 mole ratio) was slowly added into the solution of the low valent titanium compound, prepared from $TiCl_4$ and Zn(Cu), during 3 h, the cross aldol-type adduct



$$\mathrm{RCHO}\xrightarrow{\mathrm{TiCl_4/Zn(Cu)/additive/solvent}}\mathrm{R\overset{OH}{C}H-\overset{OH}{C}HR}$$

Table 1. The Effect of Solvents in the Reductive Self-coupling

R	Solvent	Temp/ °C	Additive	Yield/%
$Ph(CH_2)_2$	n-hexane	0	none	0
	toluene	0	none	0
	pyridine	0	none	0
	THF	0	none	78
	DME	0	none	85
	DME	-23	none	68
$Ph(CH_2)_2$	CH_2Cl_2	-23	DME	6
CO_2Bn	CH_2Cl_2	-23	DME	40[a)]

a) BnO_2CCH_2OH (50%) was also obtained.

was obtained in good yield (80%). While, the yield decreased to 10-20% by one portion addition of the mixture in the above reaction as shown in Table 2.

Thus, the best result in yield was obtained when the mixture of benzylglyoxylate and 3-phenylpropanal was slowly added into the solution of the low valent titanium compound and 1,2-dimethoxyethane, an additive, at -23 °C. Several examples of the present reaction are shown in Table 3. In every case, α,β-dihydroxycarboxylic acid esters were synthesized in good yields.

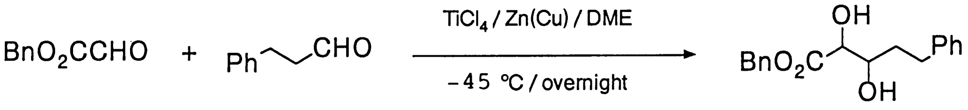
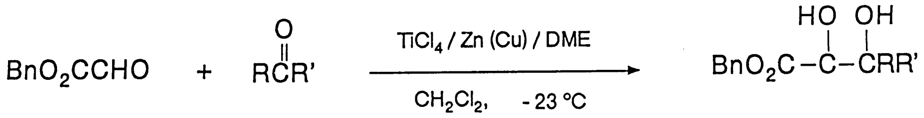


Table 2. The Effect of Addition Rate in the Cross-coupling Reaction

Molar ratio ($BnO_2CCHO/Ph(CH_2)_2CHO$)	Yield/%	Addition rate
6/1	10	all at once
6/1	80	slow addition (3h)



$$BnO_2CCHO + RC(=O)R' \xrightarrow[CH_2Cl_2,\ -23\ ^\circ C]{TiCl_4/Zn(Cu)/DME} BnO_2C-\overset{HO}{C}-\overset{OH}{C}RR'$$

Table 3. Synthesis of α,β-Dihydroxycarboxylic Acid Benzylesters

R	R'	Additive	Solvent	Temp/°C	Yield/%[a]	syn/anti[b]
$Ph(CH_2)_2$	H	DME	CH_2Cl_2	-23	84	50/50
		none	DME	-45	95	72/28
Ph	H	DME	CH_2Cl_2	-23	80	50/50
		none	DME	-45	88	82/18
$P-CH_3O-Ph$	H	none	DME	-45	90	70/30
$trans-CH_3CH=CH$	H	DME	CH_2Cl_2	-23	62	50/50
		none	DME	-45	94	55/45
Ph	CH_3	DME	CH_2Cl_2	-23	63	30/70[c]
		none	DME	-45	37	50/50[c]
Ph	Ph	DME	CH_2Cl_2	-23	57	-
$-(CH_2)_5-$		DME	CH_2Cl_2	-23	78	-

a) Determined by HPLC analysis
b) Determined by HPLC analysis and NMR spectroscopy.[7)]
c) Relative configuration not determined.

Concerning the stereochemistry, syn-selectivity was achieved in case of aromatic aldehydes and 3-phenylpropanal when a large quantity of 1,2-dimethoxyethane was used, although no stereoselectivity was observed when a small amount of 1,2-dimethoxyethane was used as an additive. While, α,β-unsaturated aldehydes showed lower selectivities.

A typical procedure for the reaction of benzylglyoxylate with a carbonyl compound is as follows: To titanium tetrachloride (4.86 mmol) in 15 ml of CH_2Cl_2 at -23 °C under argon atmosphere, DME (9.72 mmol) was added. The solution was stirred for 0.5 h at -23 °C, followed by the addition of the suspension of Zn(Cu) (15 mmol) in 15 ml of CH_2Cl_2. After stirring the suspension for 0.5 h at -23 °C, the mixture of benzylglyoxylate (2.0 mmol) and a carbonyl compound (0.4 mmol) in 8 ml of CH_2Cl_2 was added by a motor driven syringe pump during 3 h. After the addition, the mixture was further stirred overnight at -23 °C, and then quenched with saturated aqueous sodium bicarbonate. The organic layer was separated, dried over $MgSO_4$ and concentrated. The desired compound was isolated by silica gel column chromatography and/or preparative thin layer chromatography.

The general scheme of the present reaction is as follows: the low valent titanium compound preferentially reduces a glyoxylic acid ester to generate the titanium enediolate(1), which in turn attacks a carbonyl compound as a nucleophile to give the corresponding cross aldol-type adduct after hydrolysis (Fig. 1).

The most characteristic point of this reaction is that the reducing ability of the low valent titanium compound is enhanced by the addition of 1,2-dimethoxyethane, and further, that slow addition of the mixture of glyoxylic acid benzylester and a carbonyl compound to the solution of the low valent titanium compound suppresses the self-coupling reaction of the aldehyde. Consequently, desired adducts, α,β-dihydroxycarboxylic acid esters, are prepared in good yields.

It should be noted that, starting from the glyoxylic acid ester and carbonyl compounds, crossed aldol-type adducts are obtained in good yields under mild conditions by the use of the low valent titanium compound.

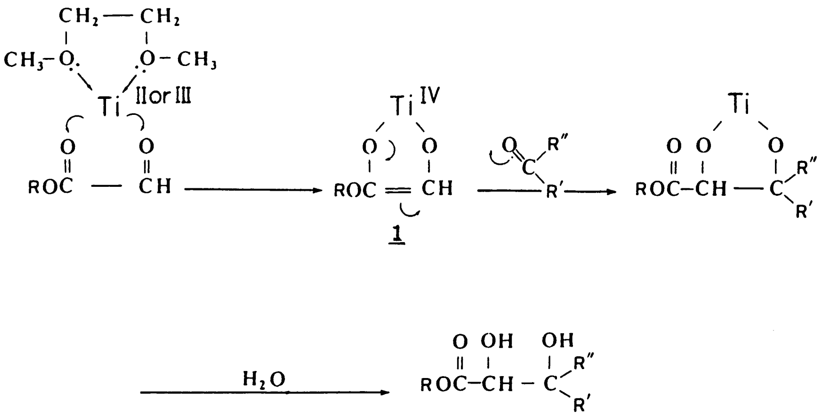


Fig. 1. Mechanism of the Reductive Cross-coupling Reaction.

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