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The Crossed Claisen Ester Condensation Mediated by Titanium(IV) Bistriflate

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The crossed Claisen ester condensation between methoxymethyl ester and methyl ester promoted by the combined use of titanium(IV) bistriflate and tertiary amine has been established.

The Claisen ester condensation is a fundamental and useful carbon-carbon bond forming reactions. However, its utility in organic synthesis has been limited because of the difficulty in controlling the direction of the reaction. For example, when the condensation is carried out between two different esters, each of which possesses an α-hydrogen, a mixture of all four products is generally obtained.[1] In order to solve this problem, esters having no α-hydrogens such as benzoates and other aromatic esters, ethyl carbonate, and ethyl oxalate, are commonly employed as acylating compounds.

One feasible solution toward these complexities is the reaction between a ketene silyl acetal and an acid chloride which afford the desired β-keto ester.[2] This method, however, requires the preceding preparation of ketene silyl acetal, and, in addition, it is difficult to manage the reaction in the case of intramolecular condensation.

In the preceding report, it was shown[3] that the Claisen ester condensation could be carried out under mild reaction conditions by using dichloro-bis(trifluoromethanesulfonato)titanium(IV) (=titanium(IV) bistriflate) as an effective promoter. Now, in the present communication, we would like to describe the crossed Claisen ester condensation can be conducted directly and efficiently between methyl ester and methoxymethyl ester.

$$\underset{\underline{1}}{R^1CO_2CH_3} + \underset{\underline{2}}{R^2CH_2CO_2CH_2OCH_3} \xrightarrow[\text{Amine}]{TiCl_2(OTf)_2} \underset{\underline{3}}{R^1COCHCO_2CH_2OCH_3}\ (R^2)$$

It is expected that when the 1:1 mixture of methyl ester (1) and methoxymethyl ester (2)[4] is treated with titanium(IV) bistriflate in the presence of tertiary amine, titanium(IV) species form strong chelate complexes with methoxymethyl ester (2) predominantly, and this is transformed into the corresponding enolate in the presence of tertiary amine, which reacts with methyl ester (1) to give the desired β-keto ester (3).

In the first place, methoxymethyl methyl adipate (4) was examined to find optimum reaction conditions. Among the various conditions screened, the use of diisopropylethylamine or N-ethylpiperidine at -23 °C gave the best results as shown in Table 1 (entries 3-5,8,9). As expected, 2-(methoxy)methoxycarbonylcyclopentanone (5), the desired β-keto ester, was obtained as the main product along with a trace amount of 2-methoxycarbonylcyclopentanone (6).

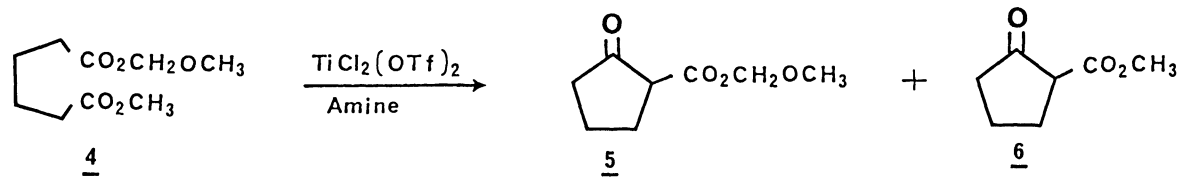

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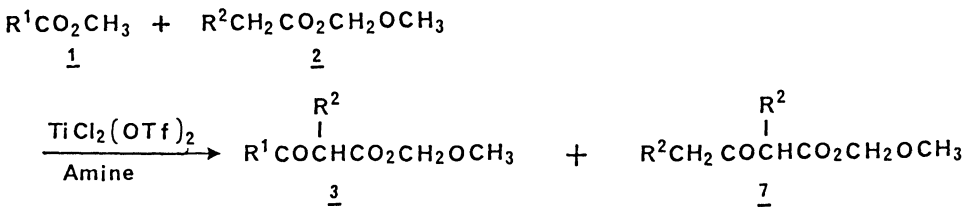
Table 1. Condensation of methoxymethyl methyl adipate (1) [a]

Entry	Amine (equiv.) vs. 4	Conditions	Yield of 5/%	Recovery of 4/%
1	Et_3N (3.0)	0 °C, 1 h	31	52
2	Et_3N (3.0)	-23 °C, 1 h	45	41
3	$(^iPr)_2NEt$ (2.0)	-23 °C, 1 h	69	22
4	$(^iPr)_2NEt$ (3.0)	-23 °C, 1 h	83	3
5	$(^iPr)_2NEt$ (3.5)	-23 °C, 1 h	82	0
6	Bu_3N (3.0)	-23 °C, 1 h	62	18
7	N-methylpiperidine (3.0)	-23 °C, 1 h	71	7
8	N-ethylpiperidine (3.0)	-23 °C, 1 h	77	5
9	N-ethylpiperidine (3.0)	-23 °C, 3 h	83	0

a) The reaction was carried out in CH_2Cl_2 and the molar ratio of $TiCl_2(OTf)_2$: 4 = 1.3 : 1.0.

Next, intermolecular condensation between methyl ester (1) and methoxymethyl ester (2) was examined. As summarized in Table 2, a variety of methoxymethyl β-keto esters were prepared under the optimum conditions found for the intramolecular reactions.

Table 2. Intermolecular ester condensation [a]



Entry	R^1	R^2	Base	Yield of 3/%[b]	Yield of 7/%[b]
1	PhCH=CH	Et	A[c]	82	5
2	PhCH=CH	Et	B[d]	76	8
3	$PhCH_2CH_2$	Et	A	83	7
4	$PhCH_2CH_2$	Et	KH[e]	18	13
5	$PhCH_2CH_2$	Et	$NaOCH_3$[e]	trace	12
6	Et	Pr	A	67	8
7	s-Bu	Et	A	57	trace
8	$PhCH_2CH_2$	Et	A	72	15
9	$PhCH_2CH_2$	$BrCH_2CH_2$	A	72	8
10	$PhCH_2CH_2$	Cl	A	45	7
11	$PhCH_2CH_2$	$^tBu(Me)_2SiOCH_2$	A	66	5

a) The reaction was carried out in CH_2Cl_2 at -23 °C for 3 h and 0 °C for 1h, and the molar ratio of 1 : 2 : $TiCl_2(OTf)_2$: amine = 1 : 1 : 1.3 : 3.0.

b) All the compounds gave satisfactory spectral data.

c) A: Diisopropylamine.

d) B: N-Ethylpiperidine.

e) KH or $NaOCH_3$ was used as a promoter in place of $TiCl_2(OTf)_2$ and amine.

As shown in Table 2, the combined use of titanium(IV) bistriflate and diisopropylethylamine affords the desired product (3) in good yield and with good selectivity.[5)]

As controlled experiments,[6)] commonly employed bases such as potassium hydride (entry 4) and sodium methoxide (entry 5) were examined in the same reaction, however, the condensation products were obtained in poor yield with low selectivity.

In addition, it is noted that the present method could be successfully applied to esters containing base sensitive functional group such as α-chloro or β-siloxy group giving the corresponding β-keto esters without loss of these functionalities (entries 10, 11).

The following example is representative: To a suspension of titanium(IV) bistriflate (208 mg, 0.50 mmol) in 1.0 ml of dichloromethane was added diisopropylethylamine (149 mg, 1.15 mmol) in 1.0 ml of dichloromethane at -23 °C under an argon atmosphere with stirring. After the mixture (brown solution) has been stirred for 10 min, a mixture of methyl 3-phenylpropionate (63 mg, 0.38 mmol) and methoxymethyl propionate (45 mg, 0.38 mmol) in 1.5 ml of dichloromethane at -23 °C. The reaction mixture was stirred at that temperature for 3 h and was allowed to warm to room temperature and stirred for 1 h. Then phosphate buffer (pH 7, 5 ml) was added, and after Celite filtration of the mixture, the aqueous layer was extracted with dichloromethane (5 ml x 2). The combined extracts were dried (Na_2SO_4) and concentrated to leave an oil. Purification on silica gel TLC (eluent: EA/HX = 1 : 5) gave methoxymethyl 2-methyl-5-phenyl-3-ketovalerate (79 mg, 83%) and methoxymethyl 2-methyl-3-ketovalerate (5 mg, 7%).

It is noted that the present method provides the first example of the crossed Claisen ester condensation between two different esters under mild acidic conditions, and that the resulting methoxymethyl β-keto ester could have wider applicability in organic synthesis.

References

1) J. March, "Advanced Organic Chemistry," 3rd ed, McGrawhill, Inc., New York (1985), pp. 437-443; H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., Menlo Park, California (1972), pp. 740-745; C. R. Hauser and B. E. Hudson Jr., Org. React., 1, 266 (1942).

2) M. W. Rathke and D. F. Sullivan, Tetrahedron Lett., 1973, 1297.

3) Y. Tanabe and T. Mukaiyama, Chem. Lett., 1984, 1867.

4) Methoxymethyl esters were prepared easily from the corresponding carboxylic acid and chloromethyl methyl ether. For example, T. W. Green, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York (1981), pp. 159-160, and other methods.

5) Attempted use of other alkoxymethyl ester (isopropoxymethyl or benzyloxy ester) did not afford more fruitful results both in yield and in selectivity.

6) These reactions were carried out according to the known procedure: D. C. Roberto and S. M. McElvain, J. Am. Chem. Soc., 59, 2007 (1937), ($NaOCH_3$); C. A. Brown, Synthesis, 1975, 326, (KH).

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