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DICHLORO-BIS(TRIFLUOROMETHANESULFONATO)TITANIUM(IV) AS AN EFFECTIVE PROMOTER IN THE CLAISEN ESTER CONDENSATION

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Inter- and intra-molecular condensation (the Claisen and the Dieckmann condensations) between ester functions have been effected by the combined use of dichloro-bis(trifluoromethanesulfonato)titanium(IV) and tertiary amine under mild conditions.

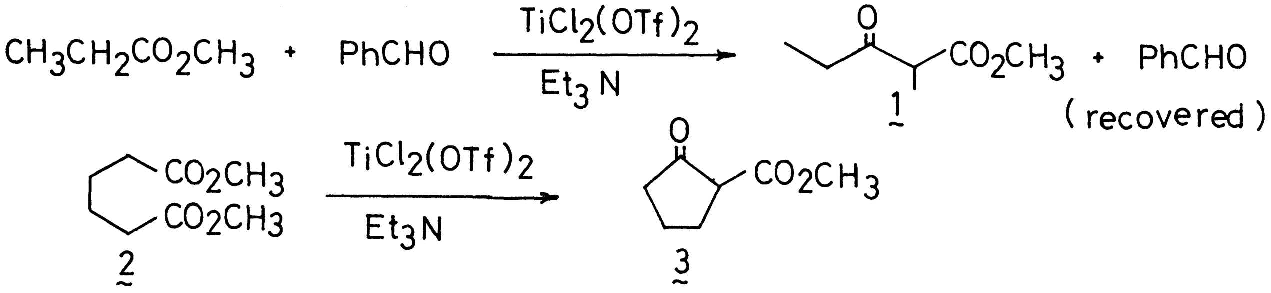
Since the discovery1) of the usefulness of dialkylbolyl trifluoromethanesulfonate (triflate)-mediated synthetic process, much attention has been attracted in the field of carbon-carbon bond forming reactions by the use of metal triflates, in particular, such as an aldol type reaction. Recently new possibilities in the aldol type reactions were widely exploited in our laboratory employing Sn(II)enolate generated by stannous(II) triflate and carbonyl compound in the presence of tertiary amine.2)

Because of their mild reaction conditions and of high regio- and stereoselectivities, these reactions have been successfully applied in the syntheses of natural products, especially of polyoxy compounds such as carbohydrates,3) and ionophore antibiotics.4)

During our continuing work on the chemistry of metal triflates, a useful C-C bond forming reaction based on dichloro-bis(trifluoromethanesulfonato)titanium(IV) was studied. In this communication, we wish to report the Claisen and the Dieckmann condensations between ester functions mediated by dichlor-bis(trifluoromethanesulfonato)titanium(IV) (= titanium(IV) bistriflate) in the presence of triethylamine. Titanium(IV) bistriflate has already been known in the literature,5) however, no example has been reported on its application in organic synthesis.

First, the addition reaction of ester onto aldehyde using titanium(IV) bistriflate was studied in order to examine the ability of titanium(IV) bistriflate to generate the corresponding enolate from ester, because stannous(II) triflate fail to promote the reaction perhaps due to the low acidity of α-proton of ester.6) The reaction of methyl propionate with benzaldehyde in the presence of titanium(IV) bistriflate and triethylamine (molar ratio of ester : aldehyde : $TiCl_2(OTf)_2$: Et_3N = 1.0 : 1.1 : 1.1 : 1.1) at 0 °C in dichloromethane for 10 h did not afford even a trace amount of the expected β-hydroxy ester after usual work up of the reaction mixture. Instead, methyl 2-methyl-3-ketovalerate (1) was obtained as a main product, though in only 36% yield.

The results led us to study the Claisen (or the Dieckmann) condensation reaction under the above mentioned reaction condition by using titanium(IV) bistriflate for the comparison with the condition commonly carried out in the basic media.⁷⁾ In the first place, dimethyl adipate (2) was chosen as the substrate and the reaction under the above mentioned conditions gave 2-methoxycarbonyl cyclopentanone (3) by intramolecular cyclization, i.e. the Dieckmann condensation.



Several solvents were screened under the same condition employing Et_3N as a base (molar ratio of $TiCl_2(OTf)_2$: substrate : Et_3N = 1.1 : 1.0 : 1.1), and 17% yield of product 3 was obtained along with 80% recovery of dimethyl adipate 2 in toluene. A trace amount of product 3 was given along with 61% and 75% recovery in ether and hexane respectively. The best result was obtained when dichloromethane was used, that is 45% yield of product 3 along with 55% recovery of 2.

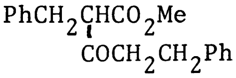
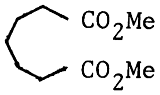
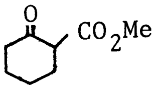
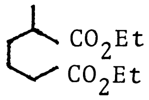
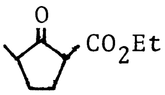
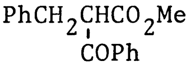
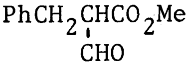
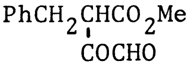
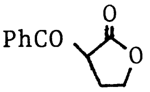
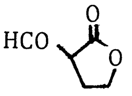
Next, we examined the effect of the bases and the molar ratio of the substrate on the yield, and it was observed that the present reaction is extremely dependent on the nature of tertiary amine. The tendency of the effects of amine is similar to that of our previous results on the aldol reaction using stannous(II) triflate.²⁾ Thus, combined use of 1.5 equiv. of titanium(IV) bistriflate and 2.2 equiv. of triethylamine in the presence of molecular sieves 4A gave the best results as shown in Table 1 (entry 12).⁸⁾

Table 1. Effect of Base and Molar Ratio on the Dieckmann Condensation a)

Entry	Base	$TiCl_2(OTf)_2$ (equiv.)	Base (equiv.)	Yield/% b)
1	Pyridine	1.1	2.2	> 5
2	CsF	1.1	2.2	0
3	N-Ethylpiperidine	1.1	2.2	30
4	$^iPr_2NEt$	1.1	2.2	45
5	DBU	1.1	2.2	0
6	2,6-Lutidine	1.1	2.2	10
7	Et_3N	1.1	1.1	35
8	Et_3N	1.1	2.2	55
9	Et_3N	1.5	2.2	71
10	Et_3N	1.1	3.3	38
11	Et_3N	1.5	3.3	48
12	Et_3n (M.S. 4A)	1.5	2.2	80

a) The reaction was carried out 0 °C for 2 h.
b) Isolated yield.

Table 2. Several Types of Ester Condensation a)

Entry	Ester(substrate)	Acylating reagent	Conditions	Yield/%	Product
1	$CH_3CH_2CO_2Me$	–	0 °C, 2 h	72	$EtCOCH(CH_3)CO_2Me$
2	$CH_3CH_2CO_2Et$	–	0 °C, 2 h	70	$EtCOCH(CH_3)CO_2Et$
3	$PhCH_2CH_2CO_2Me$	–	0 °C - r.t. 10 h	55	 $PhCH_2\underset{COCH_2CH_2Ph}{C}HCO_2Me$
4		–	0 °C - r.t. 10 h	51	
5	$^{i}PrCO_2$ Me	–	0 °C - r.t. 10 h	0	–
6		–	0 °C - r.t. 10 h	56	
7	$PhCH_2CH_2CO_2Me$	$PhCO_2Me^{c)}$	0 °C - r.t. 10 h	71	 $PhCH_2\underset{COPh}{C}HCO_2Me$
8	$PhCH_2CH_2CO_2Me$	$HCO_2Et^{c)}$	0 °C - r.t. 10 h	59	 $PhCH_2\underset{CHO}{C}HCO_2Me$
9	$PhCH_2CH_2CO_2Me$	$HCOCO_2Et^{c)}$	0 °C - r.t. 10 h	62	 $PhCH_2\underset{COCHO}{C}HCO_2Me$
10	γ-Butyrolactone	$PhCO_2Me^{c)}$	0 °C - r.t. 10 h	70	
11	γ-Butyrolactone	$HCO_2Et^{c)}$	0 °C - r.t. 10 h	52	

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a) The reaction was carried out in CH_2Cl_2 in the presence of M.S. 4A. Molar ratio of $TiCl_2(OTf)_2$: Et_3N : ester (substrate) = 1.5 : 2.2 : 1.0.

b) Isolated yield. All samples gave satisfactory ^{1}H-NMR and IR spectra.

c) Acylating reagent is 3.0 equiv. vs. ester (substrate).

The ester condensation by using several other esters under the optimum reaction conditions gave self ester condensation (the Claisen condensation) products in good yields (Table 2, entries 1 - 4), but no desired compound was detected in the case of α,α-dialkyl ester (entry 5). These results reflect on the cyclization of diethyl 2-methyladipate to afford only 2-ethoxycarbonyl-5-methylcyclopentanone without accompanying 2-ethoxycarbonyl-2-methylcyclopentanone. According to the similar procedure described in the above reaction, benzoylation, formylatoin and oxalation are also successfully performed (entries 7-11).

A typical reaction procedure is described for the reaction of methyl 2-phenylpropionate and methyl benzoate; to a suspension of titanium(IV) bistrifalte (179 mg, 0.429 mmol) and molecular sieves 4A (0.5 g) in 1.0 ml of dichloromethane was added methyl 2-phenylpropionate (47 mg, 0.286 mmol) and methyl benzoate (117 mg, 0.858 mmol) in 3.0 ml of dichloromethane at 0 °C under argon atmosphere with stirring. After the mixture (yellow suspension) was stirred for 10 min, triethylamine (64 mg, 0.630 mmol) in 1.0 ml of dichloromethane was added dropwise at this temperature. At this point, the reaction mixture became a brown solution, and was allowed to room temperature and stirred for 10 h. Then phosphate buffer at pH 7.0 was added to the reaction mixture with vigorously stirring. After celite-filtration of the mixture, the aqueous layer was extracted with dichloromethane two times, then the combined organic layer was dried over Na_2SO_4. After concentration in vacuo the resultant oil was purified by preparative thin layer chromatography (hexane : ethyl acetate = 5 : 1) to yield methyl 2-phenyl-1-benzoylpropionate (54 mg, 71%).

Thus the mild reaction condition of the present titanium(IV) bistriflate - mediated condensation reaction between ester functions is considered to have an advantage over so called classical type of the Claisen condensation, in that, this reaction proceeds under essentialy neutral condition to afford β-keto ester derivatives in fairly good yields. Further study directed towards new type of C-C bond forming reaction utilizing the characterisitcs of titanium(IV) bistriflate are currently in progress in our laboratory.

References

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2) T. Mukaiyama, R. W. Stevens, and N. Iwasawa, Chem. Lett., 1982, 353; T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984); T. Mukaiyama and N. Iwasawa, Chem. Lett., 1984, 753.

3) R. W. Stevens and T. Mukaiyama, Chem. Lett., 1983, 595.

4) For example, S. Masamune, H. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, J. Am. Chem. Soc., 103, 1568 (1981).

5) R. E. Noftle and G. H. Cady, Inorg. Chem., 5, 2182 (1966). NOTE: (i) Although the authors reported that the excess trifluoromethanesulfonic acid and other volatile by-products were removed by evaporation in vaccuo, we found that it was necessary to wash the crude precipitate with sulfuryl chloride several times to remove them before evaporation. (ii) Titanium(IV) bistriflate was an easy to handle lemmon yellow powder that can be prepared in large quantity and stored for many weeks under an inert atmosphere. Its quality could be checked by ^{19}F-NMR (solv. HMPA).

6) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1982, 1441.

7) For a review, C. R. Hauser and B. E. Hudson, Jr., Org. React., 8, 59 (1954); H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Inc., Menlo Park, California (1972), p. 734; For a recent study, C. A. Brown, Synthesis, 1975, 326.

8) The best result was obtained when triethylamine was added to the mixture of ester and titanium(IV) bistriflate. The order of the addition of reagents influences on the yield, because in the anbsence of ester titanium(IV) bistriflate probably forms a complex between triethylamine in dichloromethane at 0 °C.

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