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A Useful Method for the Preparation of Carboxylic Esters from Free Carboxylic Acids and Alcohols

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Various carboxylic esters are prepared in excellent yields from nearly equimolar amounts of free carboxylic acids and alcohols at room temperature by combined use of 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of active titanium(IV) salt together with chlorotrimethylsilane.

The formation of esters from carboxylic acids and alcohols is one of the most fundamental and important reactions in synthetic organic chemistry, and a variety of methods for the preparation of carboxylic esters are already known. Concerning the preparation of esters from nearly equimolar amounts of carboxylic acids and alcohols, DCC (dicyclohexylcarbodiimide) was developed as one of the most effective reagents which activate both carboxylic acids and alcohols. Further, there have been reported several dehydrating reagents which activate carboxylic acids in the coexistence of a base such as tertiary amines.1) On the other hand, there are few examples concerning the esterification efficiently carried out under acidic conditions from equimolar amounts of the two components. Namely, in the presence of protic acids or Lewis acids, the esterification has been generally carried out (a) by using one of the components, carboxylic acids or alcohols, in large excess or (b) by the azeotropic removal of water in order to shift the equilibrium for the completion of the carboxylic ester forming reaction. In some cases, the corresponding esters are produced in lower yields; for example, (a) when α,α-disubstituted carboxylic acids are used because of the steric hindrance of the acids or (b) when branched alcohols are used due to dehydration to form the corresponding olefins.1) Therefore, it is desired to develop a high yielding carboxylic ester forming reaction from equimolar amounts of free carboxylic acids and alcohols under mild conditions by using acidic catalysts.2) The present communication describes a highly efficient method for the preparation of esters by combined use of a substituted benzoic anhydride and a catalytic amount of an active titanium(IV) catalyst together with chlorotrimethylsilane.

Recently, an effective method for the synthesis of esters from nearly equimolar amounts of silyl carboxylates and alkyl silyl ethers via mixed anhydrides was developed by using 4-(trifluoromethyl)benzoic anhydride and an active acidic catalyst.3) In the above reaction, the use of silyl derivatives of carboxylic acids and of alcohols is essential for the completion of the esterification reaction at room temperature. In the present study, we explored the possibility of the preparation of esters from free carboxylic acids and alcohols instead of the above silyl derivatives. It was assumed that the formation of the key intermediate, the mixed anhydride, and the subsequent alcoholysis of the mixed anhydride would be smoothly promoted by using benzoic anhydride having strongly electron withdrawing groups. Then, the condensation reaction of 3-phenylpropionic acid and 1-methyl-3-phenylpropanol was tried in the presence of 4-(trifluoromethyl)benzoic anhydride and 20 mol% of active titanium(IV) catalyst generated in situ from 1 mol of $TiCl_4$ and 2 mol of $AgClO_4$. Though the reaction proceeded smoothly, alcohol was not consumed completely and the desired ester was obtained in 88% yield along with a small amount of undesirable ester, 1-methyl-3-phenylpropyl 4-(trifluoromethyl)benzoate. To improve yield and chemoselectivity, several substituted benzoic anhydrides and additives were screened. It was revealed that the desired ester is exclusively obtained when 3,5-bis(trifluoromethyl)benzoic anhydride was employed as an anhydride, but the reaction was also not completed probably due to the deactivation of the catalyst by one of the reagents (see Table 1, Entry 7).

The desired ester was obtained in 85% yield when the reaction was carried out by using 20 mol% of the titanium(IV) catalyst pretreated with 1-methyl-3-phenylpropanol for 1 h, successive addition of 3-phenylpropionic acid and 3,5-bis(trifluoromethyl)-benzoic anhydride. On the other hand, when 20 mol% of the titanium(IV) catalyst was treated with 3-phenylpropionic acid for 1 h before the esterification, the desired ester was obtained in 70% yield. The results indicate that the activity of the titanium(IV) catalyst was decreased apparently in the latter experiment. Therefore, we attempted to look for suitable reagents which serve to keep the activity of the titanium(IV) catalyst during the reaction. After screening several additives such as molecular sieves and hexamethyldisiloxane, it was found that chlorotrimethylsilane was a quite effective co-reagent to carry out the reaction. For example, in the presence of 2 mol of chlorotrimethylsilane, 1.1 mol of 3,5-bis(trifluoromethyl)-benzoic anhydride and 10 mol% of the active titanium(IV) catalyst, the reaction proceeded smoothly to afford the desired ester exclusively in 94% yield (Entry 11). The effect of chlorotrimethylsilane was so influential that the corresponding ester was obtained in high yield without accompanying the undesired ester when 4-(trifluoromethyl)benzoic anhydride was used as an anhydride instead of 3,5-bis(trifluoromethyl)benzoic anhydride (see Table 2). Thus, the desired ester was produced exclusively in nearly quantitative yield by the reaction of free carboxylic acid and alcohol in the presence of 4-(trifluoromethyl)benzoic anhydride, 10 mol% of active titanium(IV) catalyst and 0.5 mol of chlorotrimethylsilane at room temperature (Entry 4). It is assumed that a novel catalyst system is generated from the active titanium(IV) catalyst and chlorotrimethylsilane, because use of only 0.2 mol of chlorotrimethylsilane was also effective in the above reaction and other catalysts generated from $TiCl_2(OTf)_2$, $Sn(OTf)_2$ or $AgClO_4$ and chlorotrimethylsilane gave unsatisfied results in the same reaction (Entries 5-8).

Several examples of the present condensation reaction are demonstrated in Table 3. In every case, the reaction proceeded smoothly at room temperature in dichloromethane to give the corresponding esters in excellent yields from nearly equimolar amounts of free carboxylic acids and alcohols. In the cases of using hindered carboxylic acid such as pivaloic acid or branched alcohols such as menthol and cholestanol, the corresponding carboxylic esters were also produced in high yields at room temperature. Furthermore, it is noted that the present procedure is quite simple and almost pure esters are obtained just by washing the reaction mixture with saturated aqueous $NaHCO_3$.

A typical experimental procedure is described for the reaction of 3-phenylpropionic acid and 1-methyl-3-phenylpropanol; to a suspension of $AgClO_4$ (7.7 mg, 0.037 mmol), $TiCl_4$ (3.5 mg, 0.0185 mmol) and chlorotrimethylsilane (101 mg, 0.93 mmol) in dichloromethane (10 ml) were added successively a mixture of 4-(trifluoromethyl)benzoic anhydride (740 mg, 2.04 mmol) and 3-phenylpropionic acid (307 mg, 2.04 mmol) in dichloromethane (7.5 ml) and a solution of 1-methyl-3-phenylpropanol (278 mg, 1.85 mmol) in dichloromethane (2.5 ml). The reaction mixture was kept stirring for 13 h at rt, and then quenched with sat. aq. $NaHCO_3$. After the usual work up, the crude product was purified by preparative TLC on silica gel to afford 1-methyl-3-phenylpropyl 3-phenylpropionate (518 mg, 1.83 mmol) in 99% yield.

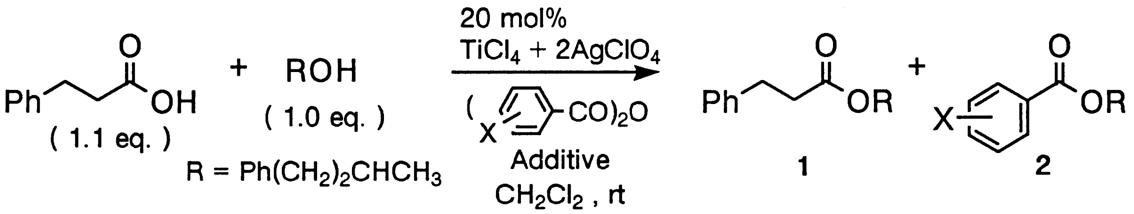


Table 1. Effect of Substituted Benzoic Anhydrides and Additives

Entry	X	Additive	Yield / %	1 / 2[a]
1	2 - F	-	82	70 / 1
2	3 - NO_2	-	72	60 / 1
3	4 - NO_2	-	57	40 / 1
4	2 - CF_3	-	88	80 / 1
5	3 - CF_3	-	87	180 / 1
6	4 - CF_3	-	88	180 / 1
7	3, 5 - $(CF_3)_2$	-	85	>200 / 1
8	3, 5 - $(CF_3)_2$	MS - 3Å	90	>200 / 1
9	3, 5 - $(CF_3)_2$	MS - 4Å	78	>200 / 1
10	3, 5 - $(CF_3)_2$	MS - 5Å	85	120 / 1
11	3, 5 - $(CF_3)_2$	Me_3SiCl (2 eq.)	94	>200 / 1
12	3, 5 - $(CF_3)_2$	$(Me_3Si)_2O$ (2 eq.)	88	>200 / 1

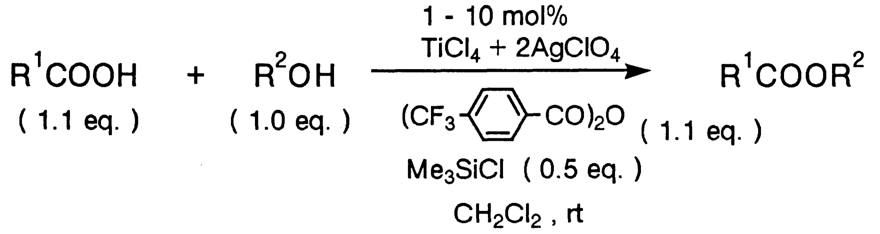
a) Determined by ^{1}H-NMR.

Table 2. Effect of Catalysts, Co-catalyst and Substituted Benzoic Anhydrides

Entry	Catalyst (amount / mol%)	X	Y[a]	Yield of 1/ %
1	$TiCl_4 + 2AgClO_4$ (10)	3, 5 - $(CF_3)_2$	2	94
2	$TiCl_4 + 2AgClO_4$ (10)	4 - CF_3	2	95
3	$TiCl_4 + 2AgClO_4$ (10)	4 - CF_3	1	96
4	$TiCl_4 + 2AgClO_4$ (10)	4 - CF_3	0.5	97
5	$TiCl_4 + 2AgClO_4$ (10)	4 - CF_3	0.2	94
6	$TiCl_2(OTf)_2$ (20)	4 - CF_3	0.2	78
7	$Sn(OTf)_2$ (20)	4 - CF_3	0.2	78 (5) [b]
8	$AgClO_4$ (20)	4 - CF_3	0.2	76 (8) [b]

a) Equivalent of chlorotrimethylsilane.
b) Yield of 1-methyl-3-phenylpropyl 4-(trifluoromethyl)benzoate.

Table 3. Synthesis of Esters by the Catalytic Condensation Reaction



Entry	R^1COOH	R^2OH	Reaction time / h	Yield / % a)
1	$Ph(CH_2)_2COOH$	BnOH	12	93
2	$Ph(CH_2)_2COOH$	CH_2=$CHCH_2OH$	0.5	92
3	$Ph(CH_2)_2COOH$	$Ph(CH_2)_3OH$	0.5	96
4	$Ph(CH_2)_2COOH$	$Ph(CH_2)_2CH(OH)CH_3$	13	97 (99) b)
5	$Ph(CH_2)_2COOH$	*c*-$C_6H_{11}OH$	12	93
6	$Ph(CH_2)_2COOH$	(-)-Menthyl-OH	13	93
7	$Ph(CH_2)_2COOH$	(+)-5α-Cholestan-3β-yl-OH	17	90
8	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_3OH$	0.5	96
9	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_2CH(OH)CH_3$	3	95
10	^tBuCOOH	$Ph(CH_2)_3OH$	0.5	95
11	^tBuCOOH	$Ph(CH_2)_2CH(OH)CH_3$	16	95
12	(E)-CH_3CH=$CHCOOH$	$Ph(CH_2)_3OH$	12	93 c)
13	(E)-CH_3CH=$CHCOOH$	$Ph(CH_2)_2CH(OH)CH_3$	12	93
14 d)	PhCOOH	$Ph(CH_2)_3OH$	12	90 (1.1) e)
15 d)	PhCOOH	$Ph(CH_2)_2CH(OH)CH_3$	12	93 (1.5) f)

a) Isolated yield. 10 mol% of catalyst was used. b) One mol% of catalyst was used.
c) When 1-ethyl-2-fluoropyridinium tetrafluoroborate was used as a condensation reagent in the presence of triethylamine, isomerization of double bond was observed (see Ref. 3).
d) 3,5-bis(trifluoromethyl)benzoic anhydride was used.
e) Yield of 3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.
f) Yield of 1-methyl-3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.

Thus, it is noted that the combined use of 4-(trifluoromethyl)benzoic anhydride (1.1 mol) and a catalytic amount of active titanium(IV) salt together with chlorotrimethylsilane (0.5 mol) provides a useful and convenient method for the preparation of carboxylic esters from free carboxylic acids and alcohols at room temperature.

References

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