An Efficient Esterification Reaction between Equimolar Amounts of Free Carboxylic Acids and Alcohols by the Combined Use of Octamethylcyclotetrasiloxane and a Catalytic Amount of Titanium(IV) Chloride Tris(trifluoromethanesulfonate)

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Various carboxylic esters are prepared in good to high yields from equimolar amounts of free carboxylic acids and alcohols by the combined use of octamethylcyclotetrasiloxane and a catalytic amount of $TiCl(OTf)_3$.

Of a number of hitherto known methods for the preparation of carboxylic esters, achievement of efficiency in the esterification reactions has always been one of the challenging topics. In order to perform the esterification in high yields by equimolar reaction of carboxylic acids and alcohols under mild conditions, coupling reactions between activated derivatives of carboxylic acids and alcohols under basic conditions have been employed.[1] On the other hand, the effective preparation of carboxylic esters by using equimolar amounts of carboxylic acids and alcohols under acidic conditions is limited and use of one of the starting materials in large excess for the completion of the reaction is generally required. Therefore, it is strongly desired to explore an efficient esterification reaction which proceeds smoothly by stoichiometric reactions of free carboxylic acids and alcohols in the presence of a suitable acidic catalyst. Recently, an effective esterification reaction between silyl carboxylates and alkyl silyl ethers via mixed anhydrides was developed by using 4-(trifluoromethyl)benzoic anhydride, a co-reagent, and an active acidic catalyst.[2] Further, the combined use of 4-(trifluoromethyl)benzoic anhydride and an active titanium(IV) catalyst together with chlorotrimethylsilane was found to provide an effective method for the synthesis of esters by using nearly equimolar amounts of free carboxylic acids and alcohols instead of the above mentioned silyl derivatives.[3]

Furthermore, a direct esterification reaction between silyl derivatives of carboxylic acids and alcohols was demonstrated by using an active silicon catalyst generated in situ from 1 mol of $SiCl_4$ and 2 mol of AgOTf in hexamethyldisiloxane as the solvent without using 4-(trifluoromethyl)benzoic anhydride.[4] Then, in order to develop a practical and efficient method for the synthesis of carboxylic esters, a coupling reaction between *free carboxylic acids and alcohols* using 2 mol of $(Me_2SiO)_4$ was studied, which worked as a kind of unique dehydrating reagent, in the presence of a catalytic amount of $TiCl(OTf)_3$.

In the first place, the reaction of 3-phenylpropionic acid and benzyl alcohol was carried out in toluene by using a catalytic amount of active silicon catalyst generated in situ from 1 mol of $SiCl_4$ and 2 mol of AgOTf which is the most suitable catalyst in the above mentioned esterification reaction. However, the desired reaction did not proceed at 50 °C and phenyltolylmethane was produced in 32% yield. After screening several Lewis acids, it was revealed that the titanium (IV) salt was effective in this reaction to afford the desired ester in a high yield without accompanying any by-products (Table 1). Next, the addition of several dehydrating reagents was tried, and $(Me_2SiO)_4$ was proved to be quite effective in improving the yield.

After examining the effect of the amount of $(Me_2SiO)_4$ on the yield, the use of 2 mol of $(Me_2SiO)_4$ gave the best result

Table 1. Effect of Lewis Acids and Dehydrate Reagents

$Ph(CH_2)_2COOH$ (1.0 eq.) + $PhCH_2OH$ (1.0 eq.) → (Catalyst; Dehydrate Reagent; Toluene; 50 °C, 6 h) → $Ph(CH_2)_2COOCH_2Ph$

Entry	Catalyst (amount / mol%)	Dehydrate Reagent	Yield / %
1	$SiCl_2(OTf)_2$ (20)[a]	-	trace (32)[e]
2	AgOTf (40)	-	no raction
3	$TiCl_2(OTf)_2$ (20)[b]	-	19
4	$TiCl_2(OTf)_2$ (20)[c]	-	30
5	$TiCl(OTf)_3$ (20)[d]	-	42
6	$TiCl(OTf)_3$ (20)[d]	MS-3Å	trace
7	$TiCl(OTf)_3$ (20)[d]	MS-4Å	no reaction
8	$TiCl(OTf)_3$ (20)[d]	MS-5Å	trace
9	$TiCl(OTf)_3$ (20)[d]	$(Me_3Si)_2O$ (3.0 eq.)	9
10	$TiCl(OTf)_3$ (20)[d]	$(Me_2SiO)_3$ (3.0 eq.)	37
11	$TiCl(OTf)_3$ (20)[d]	$(Me_2SiO)_4$ (3.0 eq.)	67
12	$TiCl_2(OTf)_2$ (20)[b]	$(Me_2SiO)_4$ (3.0 eq.)	29
13	$Sn(OTf)_2$(20)	$(Me_2SiO)_4$ (3.0 eq.)	21

[a] Generated in situ from 1 eq. of $SiCl_4$ and 2 eq. of AgOTf.
[b] Generated in situ from 1 eq. of $TiCl_4$ and 2 eq. of AgOTf.
[c] Prepared according to the procedure reported by Ref. 6.
[d] Prepared according to the procedure reported by Ref. 7.
[e] Yield of phenyltolylmethane.

(Table 2). It was assumed that $(Me_2SiO)_4$ behaved as an effective silylating reagent of carboxylic acids in the first step and the resulting silylcarboxylates in turn readily reacted with alcohols to afford the desired esters. Actually, a peak of free carboxylic proton of 3-phenylpropionic acid disappeared in the ^{1}H-NMR experiment when the carboxylic acid was treated with 2 mol of $(Me_2SiO)_4$ and 1 mol% of $TiCl(OTf)_3$ in tetrachloromethane. On the other hand, the silylation of 3-phenyl-1-propanol with 2 mol of $(Me_2SiO)_4$ and 1 mol% of $TiCl(OTf)_3$ was not observed by ^{1}H-NMR. Further, the siloxane did not interfere the titanium(IV) catalyst during the reaction as it was already shown in the previous papers where hexamethyldisiloxane worked as a good co-reagent for the efficient esterification and formylation reactions.[4,5]

Several examples of the present esterification reaction are shown in Table 3. In every case, the reaction proceeds to give the corresponding esters in good to high yields in toluene from equimolar amounts of free carboxylic acids and alcohols. It is noteworthy that the reaction in all cases takes place smoothly in

Table 2. Effect of Amounts of $(Me_2SiO)_4$

$Ph(CH_2)_2COOH$ (1.0 eq.) + $Ph(CH_2)_3OH$ (1.0 eq.) → 0.1 mol% $TiCl(OTf)_3$, $(Me_2SiO)_4$ (X eq.), Toluene, 50 °C, 18 h → $Ph(CH_2)_2COO(CH_2)_3Ph$

Entry	X	Yield / %
1	0	65
2	0.3	75
3	1.0	90
4	1.5	95
5	**2.0**	**99**
6	2.5	94
7	3.0	83
8	4.0	65

Table 3. Synthesis of Esters

R^1COOH (1.0 eq.) + R^2OH (1.0 eq.) → $TiCl(OTf)_3$ (X mol%), $(Me_2SiO)_4$ (2.0 eq.), Toluene → R^1COOR^2

Entry	R^1-	R^2-	X	Temp / °C	Time / h	Yield / %
1	$Ph(CH_2)_2$-	$Ph(CH_2)_3$-	1.0	50	18	94
2	$Ph(CH_2)_2$-	$Ph(CH_2)_3$-	**0.1**	50	18	**99**
3	$Ph(CH_2)_2$-	$PhCH_2$-	1.0	50	12	76
4	$Ph(CH_2)_2$-	$PhCH_2$-	**0.1**	50	12	**87**
5	$Ph(CH_2)_2$-	CH_2=$CHCH_2$-	1.0	50	24	77
6	$Ph(CH_2)_2$-	CH_2=$CHCH_2$-	**0.1**	50	24	**92**
7	$Ph(CH_2)_2$-	4-phenyl-*s*-butyl-	1.0	70	24	57
8	$Ph(CH_2)_2$-	4-phenyl-*s*-butyl-	**0.1**	70	48	**86**
9	$Ph(CH_2)_2$-	(-)-menthyl	1.0	70	24	50[a]
10	$Ph(CH_2)_2$-	(-)-menthyl	**0.1**	70	24	**77**[a]
11	CH_3-	$Ph(CH_2)_3$-	1.0	50	12	83
12	CH_3-	$Ph(CH_2)_3$-	**0.1**	50	12	**90**
13	$CH_3(CH_2)_3$-	$Ph(CH_2)_3$-	1.0	50	12	83
14	$CH_3(CH_2)_3$-	$Ph(CH_2)_3$-	**0.1**	50	12	**95**
15	$CH_3(CH_2)_4$-	$Ph(CH_2)_3$-	1.0	50	12	72
16	$CH_3(CH_2)_4$-	$Ph(CH_2)_3$-	**0.1**	50	12	**92**
17	$(CH_3)_3C$-	$Ph(CH_2)_3$-	1.0	70	24	78
18	$(CH_3)_3C$-	$Ph(CH_2)_3$-	**0.1**	70	24	**89**
19	Ph-	$Ph(CH_2)_3$-	1.0	70	24	86
20	Ph-	$Ph(CH_2)_3$-	**0.1**	70	24	**93**
21	C_6H_{11}-	$Ph(CH_2)_3$-	1.0	60	24	89
22	C_6H_{11}-	$Ph(CH_2)_3$-	**0.1**	60	24	**96**

[a] $[\alpha]_D^{28}$ -58.0 ° (c 1.67, $CHCl_3$)

the presence of 0.1 mol% of catalyst to afford the esters in higher yields compared with the case of using 1 mol% of the catalyst. The results indicate that better yields were obtained when lesser amounts of catalyst were used. This might be explained by considering competitive backward reaction caused by the catalyst in this equilibrium system. The proposed mechanism would be supported by the following experiment. When the hydrolysis of benzyl 3-phenylpropionate with an equimolar amount of water was carried out in the presence of 2 mol of $(Me_2SiO)_4$ and 20 mol% of $TiCl(OTf)_3$ at 50 °C for 12 h, benzyl alcohol was obtained in 9% yield while the alcohol was not detected in the case of using 0.1 mol% of $TiCl(OTf)_3$ under the same conditions.

A typical experimental procedure is described for the reaction of 3-phenylpropionic acid and 3-phenyl-1-propanol in the presence of a catalytic amount of $TiCl(OTf)_3$; to a suspension of $TiCl(OTf)_3$ (0.0019 mmol) in toluene (4 ml) was added a solution of $(Me_2SiO)_4$ (3.60 mmol) in toluene (2 ml), then a mixture of 3-phenylpropionic acid (1.90 mmol) and 3-phenyl-1-propanol (1.90 mmol) in toluene (4 ml) was added. The reaction mixture was stirred for 18 h at 50 °C and then quenched with phosphate buffer (pH=7). After the usual work up, the crude product was purified by column chromatography on silica gel to afford 3-phenylpropyl 3-phenylpropionate in 99% yield.

Thus, an efficient and simple method for the preparation of carboxylic esters from equimolar amounts of free carboxylic acids and alcohols was developed by combining the use of $(Me_2SiO)_4$ with that of a catalytic amount of $TiCl(OTf)_3$ in toluene.

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