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N,N,N',N'-TETRAMETHYLCHLOROFORMAMIDINIUM CHLORIDE AS AN EFFICIENT CONDENSATION REAGENT FOR A NOVEL ESTERIFICATION APPLICABLE TO THE MACROLIDE SYNTHESIS

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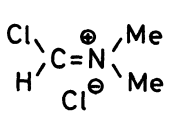
N,N,N',N'-Tetramethylchloroformamidinium chloride, prepared easily from *N,N,N',N'*-tetramethylurea and oxalyl chloride, is found to be an efficient condensation reagent for an esterification of carboxylic acids with alcohols under mild conditions in one-pot procedure, and the reagent is applied to the lactonization for macrolide synthesis from ω-hydroxycarboxylic acids.

Recently much attention has been paid to the macrolides with various physiological activities, and a number of methods for their syntheses have been reported.[1] Among them, the lactonization of hydroxycarboxylic acids is an useful method as one of intramolecular cyclizations, and various condensation reagents for the lactonization are well documented. Examples for the reagents activating carboxylic acid moiety are the methods using pyridyl disulfide-triphenylphosphine,[2] 2-chloropyridinium salt,[3] and 2,4,6-trichlorobenzoyl chloride,[4] while *N,N*-dimethylformamide dineopentylacetal[5] and a combination of triphenylphosphine and diethyl azodicarboxylate[6] are known as reagents activating alcohol moiety. In any case, these condensation reagents activate either one of two functional groups in the coexistence of hydroxy moiety and carboxylic acid moiety, and the selectively activated intermediates undergo the nucleophilic attack of another oxygen functional group. Although these reagents are useful for the lactonization of hydroxycarboxylic acids, they are not always satisfactory with respect to availability, yield or reaction conditions. Thus, a more powerful condensation reagent operated under mild conditions are required for the construction of the macrolides with many sensitive functional groups. We wish to report here an efficient one-pot procedure for the esterification from carboxylic acids and alcohols leading to the macrolide synthesis using *N,N,N',N'*-tetramethylchloroformamidinium chloride 5[7] as a powerful condensation reagent.

N,N-Dimethylchloromethyleniminium chloride 1 derived easily from *N,N*-dimethylformamide and a chlorinating reagent is known not only as a formylating reagent[8] but also as an activating reagent for carboxylic acids to give esters,[9] amides[10]



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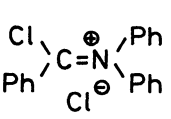

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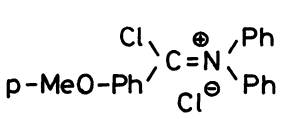

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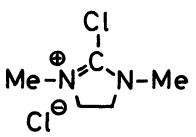

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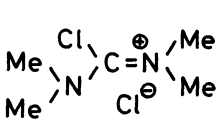

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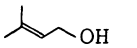
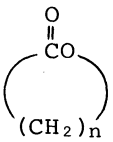
and acid chlorides,[11] while the iminium salt is reported to activate also the alcohol moiety yielding alkyl chlorides.[12] Accordingly when the iminium chloride 1 was subjected to mix with hexanoic acid and β-phenethyl alcohol in the presence of pyridine at room temperature, β-phenethyl hexanoate, β-phenethyl chloride, and β-phenethyl formate were obtained in yields of 26%, 39%, and 29%, respectively. Similarly, in the use of another iminium salt, such as *N*,*N*-diphenylchlorophenylmethyleniminium chloride 2 useful for the transformation of alcohol into alkyl chloride,[13] or *N*,*N*-diphenylchloro-*p*-methoxyphenylmethyleniminium chloride 3 useful for the ketone syntheses,[14] as a condensation reagent of the carboxylic acid and the alcohol, the corresponding ester and the chloride were simultaneously obtained. However, chloroamidinium chlorides derived from ureas were found to activate only carboxylic acid moiety giving exclusively the corresponding ester compounds without any accompaniment of the chlorinated compounds, even when the amidinium salt was used under the coexistence of equimolar amount of the carboxylic acid and the alcohol. For example, 1,3-dimethyl-2-chloroimidazolium chloride 4 derived from *N*,*N*'-dimethylimidazolidone gave β-phenethyl hexanoate in a yield of 90%, furthermore *N*,*N*,*N*',*N*'-tetrametgylchloroformamidinium chloride 5 derived from *N*,*N*,*N*',*N*'-tetramethylurea afforded the ester in a high yield of 97%, when hexanoic acid and β-phenethyl alcohol were mixed with the amidinium salts in the presence of pyridine at room temperature. Thus, *N*,*N*,*N*',*N*'-tetramethylchloroformamidinium chloride gave the best result as a powerful condensation reagent for the esterification of carboxylic acids with alcohols, which is due to the easier formation of a carboxyamidinium salt as an intermediate from carboxylic acid than a formation of an alkoxyamidinium salt from alcohol. In addition, an easy availability of the precursor, *N*,*N*,*N*',*N*'-tetramethylurea, known as one of aprotic polar solvents, is suitable for the condensation reagent.

$$\mathrm{RCOOH} + \mathrm{R'OH} \xrightarrow[\text{Base}]{5} \mathrm{RCOOR'}$$

As shown in the result of the esterification of various kinds of carboxylic acids with alcohols using *N*,*N*,*N*',*N*'-tetramethylchloroformamidinium chloride summarized in the Table, the esters from primary and secondary alcohols were rapidly prepared at room temperature in high yields. Even the esterification with *t*-butyl alcohol, which is known to be difficult, gave the corresponding ester in a yield of 77% by this method under mild conditions at room temperature, although it required for a long reaction time. The bulkiness of the substituents on carboxylic acids influenced scarcely the yields of the esters, and even pivalic acid gave the corresponding ester in a yield of 90%. When the esterification of crotonic and benzoic acids was carried out in a solution of 1,2-dichloroethane, a slight amount of chlorinated compound of the alcohol was detected. However, when the reaction was carried out in a solution of acetonitrile, the desired esters were obtained in high yields without the formation of the side-product.

A typical procedure for the esterification of hexanoic acid with β-phenethyl alcohol is as follows: Oxalyl chloride (2.2 mmol) was added to a solution of

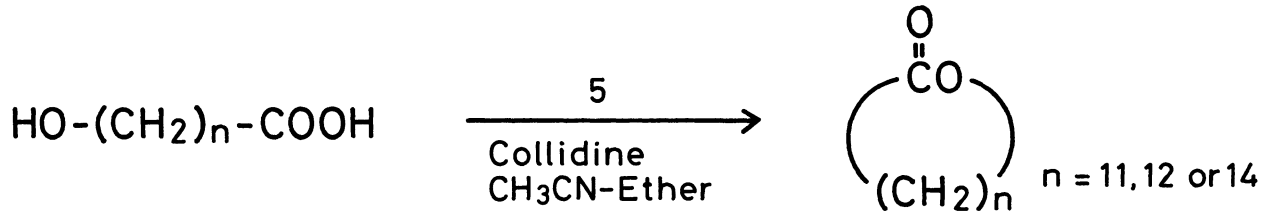
Table. Yields of the Esters by the Reaction of Various Kinds of Carboxylic Acids with Alcohols Using *N,N,N',N'*-Tetramethylchloroformamidinium Chloride[a]

Alcohol	Acid	Solvent	Base	Reaction Time	Product[b]	Yield[c] (%)
$PhCH_2CH_2OH$	n-$C_5H_{11}CO_2H$	$C_2H_4Cl_2$	Pyridine	45 min	n-$C_5H_{11}CO_2CH_2CH_2Ph$	97
$PhCH_2CH_2OH$	i-$PrCO_2H$	$C_2H_4Cl_2$	Pyridine	18 h	i-$PrCO_2CH_2CH_2Ph$	93
$PhCH_2CH_2OH$	t-$BuCO_2H$	$C_2H_4Cl_2$	Pyridine	18 h	t-$BuCO_2CH_2CH_2Ph$	90
$PhCH_2CHCH_3OH$	n-$C_5H_{11}CO_2H$	$C_2H_4Cl_2$	Pyridine	2 h	n-$C_5H_{11}CO_2CHCH_3CH_2Ph$	85
s-BuOH	n-$C_5H_{11}CO_2H$	$C_2H_4Cl_2$	Pyridine	2 h	n-$C_5H_{11}CO_2Bu$-s	79
t-BuOH	n-$C_5H_{11}CO_2H$	$C_2H_4Cl_2$	Pyridine	16 h	n-$C_5H_{11}CO_2Bu$-t	77
	n-$C_5H_{11}CO_2H$	$C_2H_4Cl_2$	Pyridine	4 h	n-$C_5H_{11}CO_2$ 	87
$PhCH_2CH_2OH$		CH_3CN	Pyridine	18 h		66
$PhCH_2CH_2OH$	$PhCO_2H$	CH_3CN	Pyridine	20 h	$PhCO_2CH_2CH_2Ph$	91
$HO-(CH_2)_{14}CO_2H$		CH_3CN-Ether	Collidine	46 h	 n = 14	90
$HO-(CH_2)_{12}CO_2H$		CH_3CN-Ether	Collidine	47 h	n = 12	68
$HO-(CH_2)_{11}CO_2H$		CH_3CN-Ether	Collidine	51 h	n = 11	54

[a] All reactions were carried out on 2 mmol scales with the same procedure as described in the text. [b] All products were identified by IR and NMR spectra after isolation by silica gel TLC. [c] Values reported are for isolated products.

N,N,N',N'-tetramethylurea (4 mmol) in 1,2-dichloroethane (3 ml), and the solution was heated at 65 °C for 2 h. To the resulting solution was slowly added a solution of hexanoic acid (2 mmol), β-phenethyl alcohol (2 mmol) and pyridine (5 mmol) in 1,2-dichloroethane (3 ml), and the reaction mixture was stirred for 45 min. The reaction was quenched by the addition of 2M HCl aq solution. The organic layer was extracted with ether, washed with $NaHCO_3$ aq solution, and dried over $MgSO_4$. After removal of the solvent, β-phenethyl hexanoate was isolated by silica gel TLC (hexane:ether = 10:1) in 97% yield.

Thus, *N,N,N',N'*-tetramethylchloroformamidinium chloride was found to be the powerful reagent activating chemoselectively carboxylic acid moiety in the coexistence of hydroxy and carboxylic acid functional groups. Further the reagent was applied to the lactonization of ω-hydroxycarboxylic acids.



In these cases, a highly diluted solution in acetonitrile-ether cosolvent system gave a good result. As seen in the Table, considerable long reaction times were needed at room temperature. An effect of some bases was examined, and collidine was found to be superior to pyridine in the lactonization. Although the yields of

the lactonization were influenced by the number of carbon atom of the lactone ring, a high yield of 90% of 15-pentadecanolide, which is called as exaltolide with a musk or amber odor, was given by the use of the present method from 15-hydroxypentadecanoic acid.

A typical procedure for the lactonization of 15-hydroxypentadecanoic acid is as follows: Oxalyl chloride (4.1 mmol) was added to a solution of *N,N,N',N'*-tetramethylurea (4 mmol) in 1,2-dichloroethane (3 ml), and the solution was heated at 65 °C for 2 h. After the solvent and excess oxalyl chloride were removed under a reduced pressure, acetonitrile (20 ml) was added to the residue. A solution of 15-hydroxypentadecanoic acid (1 mmol) and collidine (5 mmol) in acetonitrile (80 ml) and ether (100 ml) was slowly added to the solution for 10 h at room temperature. After stirring for 46 h at the same temperature, the solvent was evaporated and the reaction was quenched by the addition of 2M HCl solution. The organic layer was extracted with ether, and dried over $MgSO_4$. After removal of the solvent, 15-pentadecanolide was isolated by silica gel TLC (hexane:ether = 5:1) in a yield of 90%.

As mentioned above, *N,N,N',N'*-tetramethylchloroformamidinium chloride 5, prepared easily from *N,N,N',N'*-tetramethylurea and oxalyl chloride, is an efficient condensation reagent for the esterification of carboxylic acids with alcohols or the lactonization for macrolide synthesis. The characteristic of the present method is one-pot operation under mild conditions, and the high yields of the products.

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