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An Improved and Convenient Synthesis of Esters Using 1,1′-Carbonyldiimidazole and a Reactive Halide

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The esterification of carboxylic acids proceeded easily in a one-pot reaction with 1,1′-carbonyldiimidazole in the presence of a reactive halide under neutral reaction conditions in high yields.

Keywords——esterification; 1,1′-carbonyldiimidazole; formylation; *tert*-butyl ester; imidazolium salt; one-pot reaction

1-Acylimidazoles are effective acylation reagents,[1] but their ability to acylate alcohols is weak. Recently several improved methods for the reaction of alcohols with 1-acylimidazole have been reported. These methods can be grouped into two classes, *i.e.*, activation of the alcohols and activation of the 1-acylimidazoles. The former approach involves esterification in the presence of catalytic amounts of sodium or potassium *tert*-butoxide[2] or an equimolar amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[3] The latter involves esterification in the presence of an equimolar amount of *N*-bromosuccinimide (NBS).[4] However, these methods

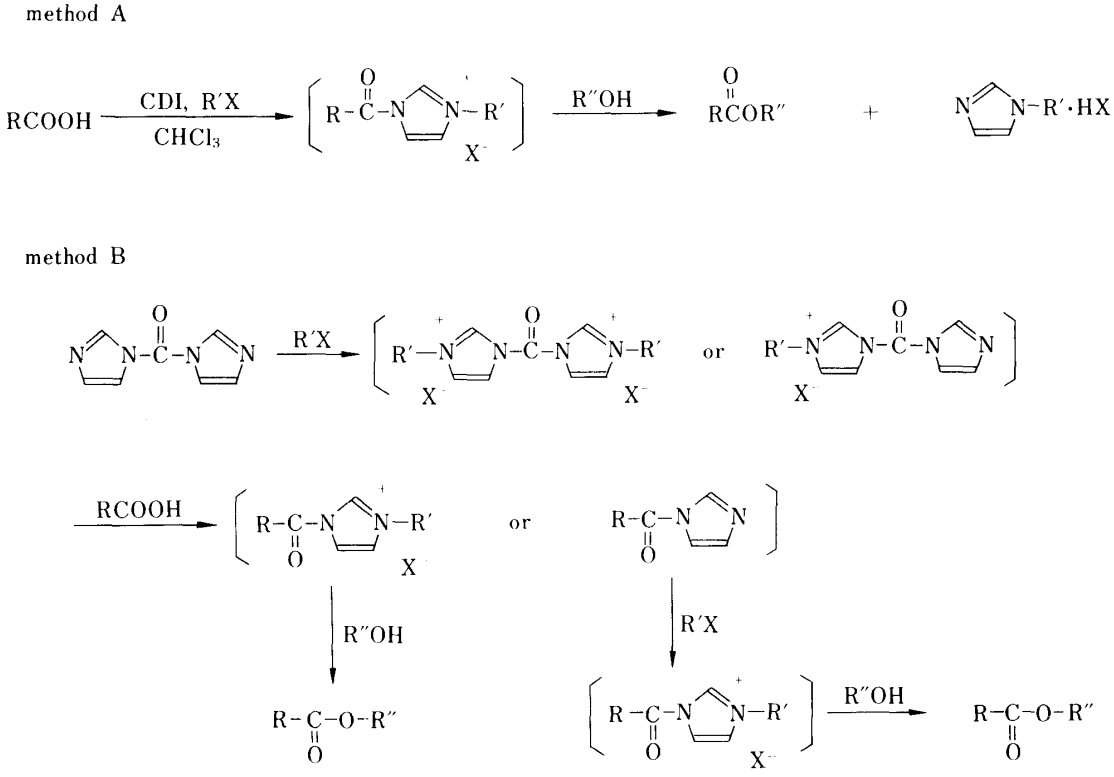


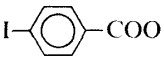
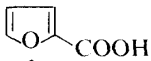
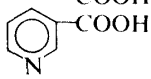
Chart 1

are not always satisfactory because of the formation of several by-products or low yields in the synthesis of sterically hindered esters. Previously, we reported that 1-acyl-3-substituted imidazolium salts were powerful acylating agents for alcohols.[5] This reaction is also an example of the activation of 1-acylimidazoles.

We report here an improved and convenient one-pot synthesis of esters from carboxylic acids with 1,1′-carbonyldiimidazole (CDI) in the presence of a reactive halide (Chart 1). Thus, the carboxylic acids were treated with CDI (1 eq) and a reactive halide (2—5 eq) such as allyl bromide or methyl iodide in chloroform, and then alcohols were added [method A], or CDI was treated with a reactive halide (2 eq) in chloroform or acetonitrile, and then the carboxylic acids (1 eq) were added to the solution followed by addition of the alcohols [method B] to afford the corresponding esters in high yields.

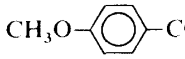
As shown in Table I, these carboxylic acids were converted to the corresponding esters in high yields by method A or B, but carboxylic acids having functional groups which can be alkylated by an excess of reactive halide, such as nicotinic acid, should be esterified by method B. Table II shows the results of the esterification with an excess of *tert*-butanol. The corresponding *tert*-butyl esters were formed in high yields under heating, and highly sterically hindered 2-phenyl-2-propyl pivalate was also obtained in 90% yield. In the reaction without allyl bromide, the yields of the esters were very low. On the other hand, the method using

Table I. Esterification of Carboxylic Acids

RCOOH	Method	R″OH[a]	Reaction conditions	RCOOR″ Yield (%)
$PhCH_2CH_2CH_2COOH$	A	EtOH	r.t. 2 h	86
	B	EtOH	r.t. 4 h	90
$PhCH_2OCONHCH(CH_3)COOH$	A	EtOH	r.t. 1 h	95
$CH_3COCH_2CH_2COOH$	A	EtOH	r.t. 2 h	88
$PhC\equiv CCOOH$	A	EtOH	r.t. 1 h	84
$CH_3CH=CHCH=CHCOOH$	A	MeOH	r.t. 2 h	95
	A	EtOH	r.t. 2 h	93
	A	EtOH	r.t. 1 h	95
	B	EtOH	r.t. 2 h	75

a) Excess of alcohol was used.
r.t. = room temperature.

Table II. Esterification with *tert*-Butanol

RCOOH	Reaction[a] conditions	$RCOOC(CH_3)_3$ Yield (%)
	Reflux 3 h	80 (< 5)[b]
$PhCH=CHCOOH$	Reflux 3 h	80
$CH_3CH_2\underset{\displaystyle Ph}{\overset{\displaystyle |}{C}}HCOOH$	Reflux 10 h	95
$PhCH_2CH_2CH_2COOH$	Reflux 10 h	95 (< 5)[b]
$(CH_3)_3CCOOH$	Reflux 6 h	90

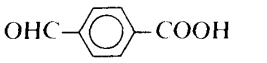
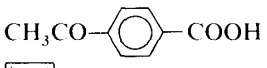
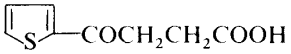
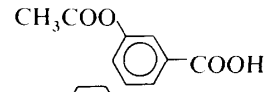
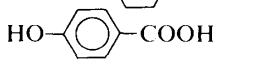
a) The reaction was carried out by method A using allyl bromide and an excess of *tert*-butanol.
b) The reaction was carried out in the absence of allyl bromide.

sodium *tert*-butoxide or NBS is not applicable to an alkanoic acid having one or two H atoms at the C-α atom because of the formation of several by-products, and the method using DBU cannot be applied to sterically hindered esters such as *tert*-butyl pivalate. As can be seen in Table II, the esterification of carboxylic acids having one or two H atoms at the C-α atom required longer reaction times, but the reason for this is not clear.

Table III shows the results of the esterification of the carboxylic acids having a reactive functional group such as a formyl, acetoxy, or hydroxyl group. 4-Formylbenzoic acid, which formed the acetal with hydrogen chloride–ethanol, was esterified to ethyl 4-formylbenzoate in 79% yield. The esterification of 3-acetoxybenzoic acid proceeded without hydrolysis of the acetoxy group in high yield, but the esterification with hydrogen chloride-methanol gave only methyl 3-hydroxybenzoate. 4-Hydroxybenzoic acid was esterified to methyl 4-hydroxybenzoate by using 2 eq of CDI in 95% yield without protection of the hydroxyl group. As shown in Table IV, the formylation of *p*-cresol and primary or secondary alcohol also proceeded in high yields. However, this method is not applicable to *tert*-alcohols because of the formation of several by-products.

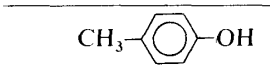
The advantages of this reaction are (1) the esters can be obtained directly from carboxylic acids by using commercially available reagents (CDI and a reactive halide such as allyl bromide or methyl iodide) in a one-pot reaction, (2) the reaction conditions are mild and the reaction proceeds in neutral medium, and (3) the resultant esters are easily isolated and

Table III. Esterification of Carboxylic Acids Having a Reactive Functional Group

RCOOH	R″OH[a]	Reaction[b] conditions	RCOOR″ Yield (%)
	EtOH	Reflux 1 h	79
	EtOH	Reflux 1 h	95
	EtOH	r.t. 1 h	95
	MeOH	r.t. 2 h	95
	MeOH	r.t. 2 h	95[c]

a) Excess of alcohol was used.
b) The reaction was carried out by method A using allyl bromide.
c) 2 eq of CDI was used.
r.t. = room temperature.

Table IV. Formylation of Alcohols and Phenols

ROH	Reaction[a] conditions	ROCHO Yield (%)
	r.t. 3 h	83
$PhCH_2CH_2OH$	r.t. 1 h	95
$Ph(CH_2)_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_3$	r.t. 4 h	95

a) The reaction was carried out by method A using allyl bromide and an equimolar amount of formic acid.
r.t. = room temperature.

purified by a simple procedure. Thus, the reaction should be generally useful for the synthesis of various esters.

Experimental

The infrared (IR) spectra were obtained with a Hitachi 260-10 infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-22 high-resolution nuclear magnetic resonance spectrometer in $CDCl_3$ with Me_4 Si as an internal standard. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed with a Yanaco MT-2 CHN Corder.

General Procedure for Esterification——Method A: A solution of a carboxylic acid in dry $CHCl_3$ was treated with 1,1′-carbonyldiimidazole (1 eq) and an excess of a reactive halide (allyl bromide or methyl iodide; 4—5 eq), and the mixture was stirred for 0.5—1 h at room temperature (carbon dioxide gas was generated immediately). Then an alcohol (1 eq or excess amounts) was added to the solution and the whole was stirred at room temperature or under reflux for 1—10 h. The reaction solution was concentrated under reduced pressure and the residue was dissolved in ether or ethyl acetate. The solution was washed with dil. HCl, aq. $NaHCO_3$, and water, then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by recrystallization or column chromatography.

Ethyl 3-Phenylpropionate——A stirred solution of 3-phenylpropionic acid (164 mg; 1 mmol) in dry $CHCl_3$ (5 ml) was treated with 1,1′-carbonyldiimidazole (162 mg; 1 mmol), and then allyl bromide (0.43 ml; 5 mmol) was added. The mixture was stirred for 1 h, then ethanol (1 ml) was added and the whole was stirred at room temperature for 2 h. The reaction solution was concentrated under reduced pressure and the residue was treated as usual to give ethyl 3-phenylpropionate (165 mg; 86%) as colorless oil. IR (neat): 1725 (C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, CH_3), 1.95 (2H, quin, CH_2), 2.31 (2H, t, CH_2), 2.65 (2H, t, CH_2), 4.12 (2H, q, CH_2), 7.1—7.3 (5H, m, aromatic-H). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.25; H, 8.55.

General Procedure for Esterification——Method B: A mixture of 1,1′-carbonyldiimidazole (1 eq) and a reactive halide (2 eq) in dry $CHCl_3$ or dry CH_3CN was stirred for 2 h at room temperature or under heating. A carboxylic acid (1 eq) was added to the solution (carbon dioxide gas was generated immediately), and then an alcohol was added. The mixture was stirred at room temperature or under reflux for 1—10 h. The reaction solution was concentrated under reduced pressure and the residue was treated as usual to obtain the ester.

Ethyl Nicotinate——A mixture of 1,1′-carbonyldiimidazole (810 mg; 4.9 mmol) and allyl bromide (1.2 g; 10 mmol) in dry CH_3CN was stirred for 2 h at room temperature. Nicotinic acid (600 mg; 4.87 mmol) was added, followed by ethanol (3 ml).

The mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure. The residue was treated as usual to give ethyl nicotinate (552 mg; 75%) as a colorless oil. IR (neat): 1720 (C=O)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, CH_3), 4.42 (2H, q, CH_2), 7.41 (1H, m, aromatic-H), 8.30 (1H, m, aromatic-H), 8.78 (1H, m, aromatic-H), 9.24 (1H, m, aromatic-H). *Anal.* Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.33; H, 5.89; N, 9.03.

The esters listed in Tables I, II, III, and IV were prepared by method A or B.

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