CHEMISTRY LETTERS, pp. 1819-1820, 1983. © The Chemical Society of Japan 1983

1,1'-OXALYLDIIMIDAZOLE, A NEW REAGENT FOR ACTIVATION OF CARBOXYLIC ACID

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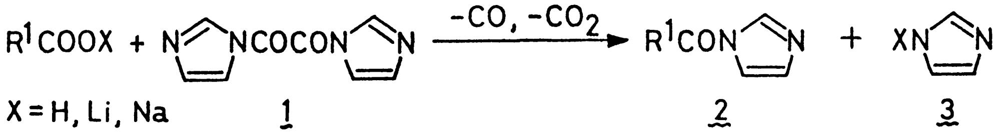
Carboxylic acids and their salts are converted into the 1-acylimidazoles by the title reagent. This reaction is applied for esterification of fatty acids.

The activation of carboxylic acids is an important chemical operation. Various methods have been reported for the purpose. The reaction of 1-acylimidazoles1) can be carried out under mild conditions and is widely applicable for organic synthesis. However, only a few procedures have been known for the preparation of imidazolides.1,2) Described herein is an effective new reagent for the conversion of carboxylic acids and their salts into the corresponding 1-acylimidazoles.



Reaction of oxalyl chloride with 2 equivalents of 1-trimethylsilylimidazole (method A)3,4) or 2 equivalents of 1H-imidazole and 2.7 equivalents of a tertiary amine (method B)5) gave 1,1'-oxalyldiimidazole (1) in high yields. Method A is suitable for isolation of 1 and B is suitable for a large scale reaction. Reaction of 1 and 1 equivalent of carboxylic acids proceeded in chloroform or dichloromethane at 25—45 °C for 1—2 h to give pure 1-acylimidazoles (2). During the reaction, oxalic acid moiety of the reagent escaped as carbon mono- and dioxide. After the starting material was consumed, there were remained only 2 and imidazole (3, X=H) in the reaction mixture. Then the imidazolide was transformed into the ester in one pot upon treatment with an alcohol. When reaction of 2 and an alcohol was slow, potassium *t*-butoxide or sodium imidazolide was used as a catalyst.1) Lithium and sodium carboxylates were also converted into their esters by the action of 1 in DMF at 60 °C followed by addition of an alcohol. In these cases, the esterification proceeded more smoothly than the case of acids. Lithium or sodium imidazolide (3, X=Li, Na), which was formed in situ, acted as the catalyst for the reaction of 2 and an alcohol. This is the first example to convert metal caboxylates into 1-acylimidazoles directly. As this procedure can be carried out under neutral to weak basic conditions, 1 is suitable for the condensation reaction of acid or base sensitive multifunctionalized substrates. For example,

Table 1. Esterification by Using 1,1'-Oxalyldiimidazole (1)

Run	Substrate	Method	Conditions[a)]		Product (% yield[b)])
			Solvent	Temp (°C)	
1	linoleic acid	A	$CHCl_3$	45	methyl linolate (79)
2	linoleic acid	A	CH_2Cl_2	25	methyl linolate (63)
3	linolenic acid	A	$CHCl_3$	45	methyl linolenate (78)
4	arachidonic acid	A	$CHCl_3$	45	methyl arachidonate (72)
5	$C_6H_5C{\equiv}CCOOH$	A	$CHCl_3$	45	$C_6H_5C{\equiv}CCOOCH_3$ (78, 91[c)])
6	$CH_3CH(OAc)CH_2COOH$	A	$CHCl_3$	45	$CH_3CH(OAc)CH_2COOCH_3$ (71[c)])
7	lithium linolate	A	DMF	60	methyl linolate (72)
8	sodium linolate	A	DMF	60	methyl linolate (85)
9	methyl hydrogen glutalate	A	$CHCl_3$	45	methyl ethyl glutalate (76)
10	*N*-acetylglycine	A	$CHCl_3$	45	*N*-acetylglycine methyl ester (66)
11	linoleic acid	B	$CHCl_3$	40	methyl linolate (73)

[a)] Conditions of 1-acylimidazole formation. [b)] Unless otherwise stated the yield means isolated yield by column chromatography on silica gel. [c)] Yield determined by gas chromatography.

methyl esters of polyunsaturated fatty acids such as linoleic acid (C18, Δ2), linolenic acid (C18, Δ3), and arachidonic acid (C20, Δ4) were prepared in good yields. The results are summerized in Table 1.

The following procedure for esterification of a carboxylic acid is representative. To a suspension of 1 (22 mg, 0.12 mmol) in dry chloroform (0.3 ml) was added linoleic acid (33 mg, 0.12 mmol) at 45 °C. After 1 h heating, gas evoluation ceased, the solution of 1-linoleoylimidazole was treated with methanol (0.1 ml) at room temperature for 4 h. Gas chromatographically pure methyl linolate (28 mg, 79%) was obtained by a column of silica gel eluting with 5% ethyl acetate in petroleum ether.

I acknowledge professors Ryoji Noyori and Sadao Matsuura of this university for kind permission to use NMR and IR spectroscopic instruments.

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4) To a solution of 1-trimethylsilylimidazole (7.0 g, 50 mmol) in dry benzene (80 ml) was added a mixture of oxalyl chloride (3.0 g, 24 mmol) and benzene (30 ml) over 1 h at 25 °C. After 80 h, 1 (4.4 g, 97% yield, 87—92 °C dec.) was obtained as pale yellow powder. Reaction of 1 and large excess of ethanol gave diethyl oxalate in 87% yield. The activity of 1 could be determined by this reaction.

5) To a mixture of 1H-imidazole (28 mg, 0.40 mmol), diisopropylethylamine (0.1 ml, 0.55 mmol), and chloroform (0.6 ml) was added oxalyl chloride (27 mg, 0.20 mmol) at -10 °C. After 15 min, the obtained yellow solution was employed in the following reaction.

(Received September 12, 1983)